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INJECTIONS OF HIGHLY CONCENTRATED LIVER EXTRACT IN TREATMENT OF IDIOPATHIC ULCERATIVE COLITIS

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Innumerable therapeutic agents have been advocated for the treatment of idiopathic ulcerative colitis. None of them has proved satisfactory, and few have proved of the slightest benefit. The oral administration of liver extract has been tried in the past, apparently with the usual lack of success.[1] It was not mentioned by Bargen or by those physicians discussing his most recent report on the therapy of ulcerative colitis,[2] nor was it mentioned in his report on the treatment of the anemia which commonly accompanies this disease.[3] Buie [4] in his recent textbook on proctology did not mention the use of liver in the treatment of ulcerative colitis. As a new form of highly concentrated liver extract for parenteral use is now available, this has been tried in the treatment of 8 patients with colitis, 7 of whom presented classic examples of the ulcerative type of unknown cause. Gratifying results were obtained in every instance with possibly 1 exception.

REPORT OF CASES

CASE 1.—*Chronic ulcerative colitis, with marked emaciation, spruelike diarrhea and recurring iritis; recovery following liver therapy.*

History.—R. F. Y. aged 43 years, formerly an insurance broker, was seen at home on Oct. 2, 1937, complaining of abdominal pains and trouble with his bowels. He had been in and out of army and veterans' hospitals for eleven years because of ulcerative colitis and iritis. Appendicostomy was performed in 1930, and for

From the Department of Medicine, Stanford University Medical School.

1. Mackie, T. T.: Ulcerative Colitis: The Factor of Deficiency States, J. A. M. A. **104**:175 (Jan. 19) 1935.

2. Bargen, J. A.: Medical Management of Chronic Ulcerative Colitis, Proc. Roy. Soc. Med. **30**:351, 1937.

3. Garvin, R. O., and Bargen, J. A.: The Hematologic Picture of Chronic Ulcerative Colitis: Its Relations to Prognosis and Treatment, Am. J. M. Sc. **193**: 744, 1937.

4. Buie, L. A.: Practical Proctology, Philadelphia, W. B. Saunders Company, 1938.

four months the bowel was irrigated through the stoma, which subsequently closed completely. He felt improved for two years after that but gradually became bedridden, owing to loss of weight and strength. He had abdominal soreness and cramps alternating with periods of diarrhea. In late years the stools when loose were often bulky, foul and foamy. Severe iritis occurred once or twice a year, usually during the periods of constipation. Numerous examinations of stools all failed to show amebas. Repeated proctoscopic examinations revealed ulceration of the bowel. Early and recent roentgenograms of the intestines showed a narrowed, smooth colon from the splenic flexure to the rectum. Agglutination tests of the blood did not reveal dysentery bacilli. A histamine test revealed achlorhydria. Results of tests of the urine, blood counts and a Wassermann test of the blood were not remarkable. His disease ran a course of remissions and exacerbations, but no form of treatment proved of any real benefit.

Examination.—When he was first seen he was emaciated and weighed only 106 pounds (48 Kg.). The left eye was badly inflamed. The whole abdomen was tender to pressure, and the descending colon was palpable and tender. He was not having any bowel movements except after oil enemas. The stool was unformed and oily and contained large amounts of mucus, but no gross or occult blood was present.

Treatment and Course.—Treatment was started at home. A high caloric diet was ordered, and liver therapy was given. He received one intramuscular injection of liver extract a week for the first month, alternating 5 cc. of a nonconcentrated extract [5] with 1 cc. of a highly concentrated extract.[6] Thereafter the dose of the nonconcentrated extract was reduced to 3 cc., and the interval between injections was lengthened to two weeks. After four months the dose of the concentrated extract was reduced to 0.5 cc. He received only one injection in March 1938, when the use of the nonconcentrated extract was discontinued. Five-tenths cubic centimeter of the concentrated extract was given regularly every two weeks thereafter. There was diarrhea during the first two weeks of therapy, from six to eight semiformed foul stools being passed daily. During the next two weeks an average of three to four stools was passed daily. During the next two weeks three to four stools were passed per day; they were better formed and were no longer foul smelling. He felt much stronger, was up and about a little and had much less abdominal discomfort. Since Jan. 1, 1938, there has usually been only one well formed bowel movement daily, and he has been able to come to the office for treatments. He gained 12 pounds (5.4 Kg.) during the first month of liver therapy. Since then his weight has risen from 118 to 127 pounds (53.5 to 57.6 Kg.). The iritis improved rapidly, so that he was able to read by the end of October 1937, and all signs of inflammation disappeared shortly thereafter. He has had no recurrence of the iritis. Proctoscopic examination on May 18, 1938, revealed a normal-appearing intestinal wall except for an area of hemorrhage

5. The product used was campolon, prepared by the Winthrop Chemical Company. It is a brand of purified solution of liver U. S. P. and contains approximately 5 units of anti-pernicious-anemia principle per cubic centimeter. The preparation has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

6. The product used was reticulogen (parenteral liver extract with vitamin B_1, Lilly). Each cubic centimeter, according to the manufacturer, contains not less than 20 units of the anti-pernicious-anemia principle and not less than 1,000 international units of vitamin B_1. The preparation has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

the size of a dime. No ulcers were present. Roentgen examination after a barium sulfate enema on the same day showed a smooth outline of the colon in the region of the splenic flexure, but elsewhere the mucosal pattern appeared normal. The sedimentation rate of the blood was 11 mm. in one hour, and the differential neutrophil count was normal.

His general condition has so improved during the past eight months that he is contemplating returning to his work, after eleven and one half years of invalidism.

Comment.—The remarkable improvement in the patient's condition has occurred after years of gradual decline and could hardly have been irrespective of liver therapy.

CASE 2.—*Severe ulcerative colitis of a year's duration in a young adult; excellent relief with liver therapy.*

History.—E. F., a 21 year old man, a saxophone player, suffered almost continuously from dysentery for one year, gradually lost almost 50 pounds (22.7 Kg.) in weight and had to cease work. He frequently had low grade fever. The stools were rarely formed and usually showed blood, pus and mucus. No amebas were present. Cultures of the stools failed to reveal dysentery bacilli or Bargen's diplococcus. Agglutination tests of the blood gave a negative reaction for dysentery bacilli. Repeated proctoscopic examinations revealed ulceration and edema of the lower portion of the bowel and at one time suppurative lesions. Roentgenograms of the colon after a barium sulfate enema revealed that the sigmoid flexure and the lower descending portion were poorly haustrated, irritable and tender. The mucosal pattern suggested the presence of small ulcers. A histamine gastric test meal showed free acid. The blood count was normal (except for leukocytosis following sulfanilamide therapy), and the urine was normal. The Wassermann test of the blood gave a negative reaction. Treatment with prolonged rest in bed; a high caloric, high vitamin and low residual diet; yeast and cod liver oil; liver and iron by mouth; sulfanilamide by mouth, and injections of Bargen's vaccine proved unavailing. He had a brief period of improvement after treatment with pyrexia from typhoid vaccine and 30 cc. of nonconcentrated liver extract [5] while in the hospital for a week in August 1937. He required ½ to 1 ounce (15 to 30 cc.) of camphorated tincture of opium daily to obtain some relief from abdominal cramps and diarrhea. He grew progressively weaker, and in November dyphagia, moderate stomatitis and edema of the ankles developed. Ileostomy was contemplated.

Treatment and Course.—The patient was in bed constantly while at home and was barely able to make an occasional visit to the office. Largely on account of the stomatitis he was given an injection of concentrated liver extract [6] on Nov. 30, 1937. He was having an average of ten watery bowel movements a day with great tenesmus at this time and weighed only 110 pounds (50 Kg.). The temperature reached 100 or 101 F. daily. He received two more injections of liver extract during the next two weeks before he began to show marked improvement. Chart 1 correlates his progressive recovery, as shown by the gain in weight and the disappearance of dysentery, with the injections of concentrated liver extract from Nov. 30, 1937, to May 26, 1938. During the third and fourth weeks of treatment the dysphagia and stomatitis disappeared, his appetite increased enormously, the edema of the ankles was much improved, the stools became formed and free from blood and pus and contained only small flecks of mucus, tenesmus no longer occurred and he gained 15 pounds (6.8 Kg.) in weight.

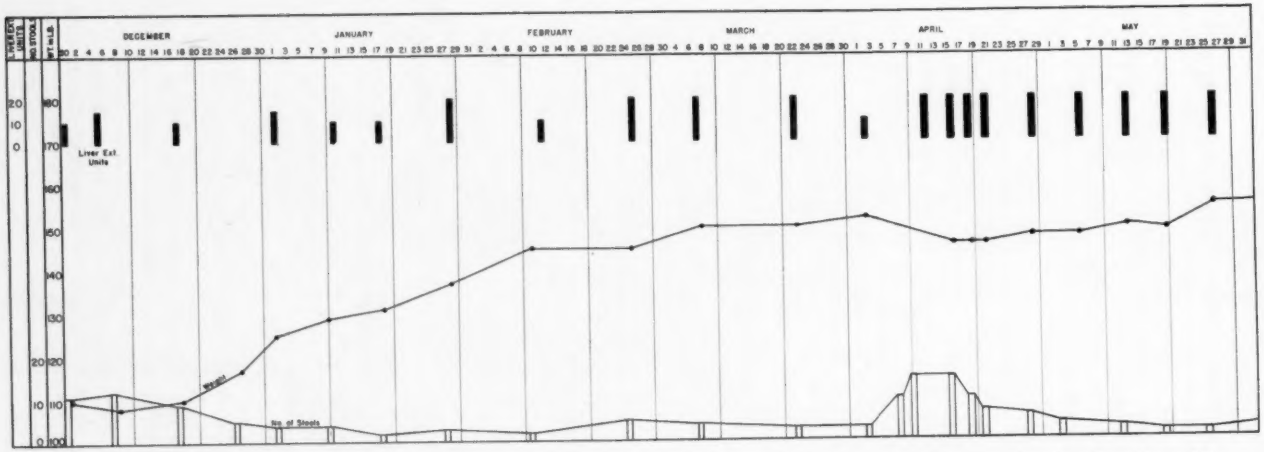

Chart 1 (case 2).—Correlation of parenteral liver therapy and clinical improvement in a case of severe chronic ulcerative colitis, as shown by cessation of diarrhea and gain in weight. A slight exacerbation of diarrhea late in February and a severe one in April followed reductions in the dose of liver extract.

During the next month, January 1938, he became active and was able to work two nights a week. He gained 12 pounds (5.4 Kg.) more. During the middle of February he felt so well he worked late every night for a week. The dose of liver was reduced at the same time, and he failed to gain weight during the two subsequent weeks and showed an increase in the number of bowel movements, to four or five a day, with occasional tenesmus and a little discharge of mucus. The dose was increased, and the symptoms cleared up, although he had an average of three to five formed movements a day during March. Another examination after a barium enema on March 29, showed a condition similar to the one observed nine months previously, except that there was no tenderness or suggestion of ulceration. A proctoscopic examination on March 30 revealed normal-appearing mucosa in the lower portion of the bowel except for three small areas of localized hemorrhagic proctitis in the lower portion of the sigmoid flexure. No ulcers were present.

On April 4 he weighed 158 pounds (71.7 Kg.), felt well and was working regularly. The dose of liver was again reduced, to 0.5 cc.; within a few days he lost his appetite, and the diarrhea became severe, with ten to fifteen watery discharges. He lost 6 pounds (2.7 Kg.; chart 1). Abdominal cramps were marked, and his temperature rose to 102 F. on April 15. He received three injections of concentrated liver extract[6] (each of 1 cc.) during the week from April 11 to 18. He was better by April 21, when he had another injection of 1 cc. During the following week the stools became formed, the cramps entirely disappeared, his appetite returned and he gained 4 pounds (1.8 Kg.) in weight. He still had five or six stools daily. A week later he was as well as ever, and the number of stools was reduced to three a day. He remained well during May, receiving one dose of 1 cc. of concentrated liver extract[6] every seven days. On May 31 the sedimentation rate was 7 mm. in one hour, and the differential neutrophil count was normal.

Comment.—The return to health and normal activity of this young man after a year of severe colitis paralleled the administration of large doses of liver. It is noteworthy that each of the two relapses shown in chart 1 followed a reduction in the amount of concentrated liver given.

CASE 3.—*Hemorrhagic ulcerative colitis with anemia of two months' duration; rapid recovery with liver therapy.*

History.—A. L. S., aged 42 years, a laborer, was first seen in the hospital on Feb. 16, 1938, complaining of diarrhea and weakness. Ten years previously he was in an army hospital for an attack of diarrhea, which lasted nine weeks and cleared up completely. He was told that the illness was due to amebas. He had no further gastrointestinal disorder until seven weeks before admission to the hospital. Diarrhea gradually developed until he was having twelve to fifteen watery discharges daily containing blood and mucus. Abdominal pains were severe at the time of defecation. He had lost 25 pounds (11.3 Kg.) in weight and had grown pale and so weak that he could not get out of bed. He had just completed a ten day course of treatment with emetine hydrochloride, without any improvement.

Examination.—He was emaciated and sallow. His temperature was normal. The six stools examined failed to show any Endamoeba histolytica. No dysentery bacilli were found on culture of the stool, and agglutination tests for the bacilli gave a negative reaction. A blood count showed 55 per cent hemoglobin, 2,700,000 erythrocytes and 9,000 leukocytes, with a normal distribution. The urine was

normal. Wassermann and Kahn tests of the blood gave negative reactions. Proctoscopic examination revealed a number of small ulcers with grayish bases in a dark red, velvety, edematous mucosa, which oozed blood readily. Roentgen examination of the bowel was unsatisfactory as the patient could not retain the barium enema.

Course and Treatment.—The patient took nourishment poorly. Tincture of opium reduced the bowel movements to about eight daily; otherwise his wretched condition was unrelieved, and he continued to lose weight.

On February 23 treatment with concentrated liver extract [6] was started, the patient receiving 0.5 cc. every other day intramuscularly. The relation of this treatment to the number and the type of stools passed and to his body weight is graphically shown in chart 2. A marked reduction in the diarrhea occurred within ten days, and he had less pain; but on March 2 severe renal colic developed on

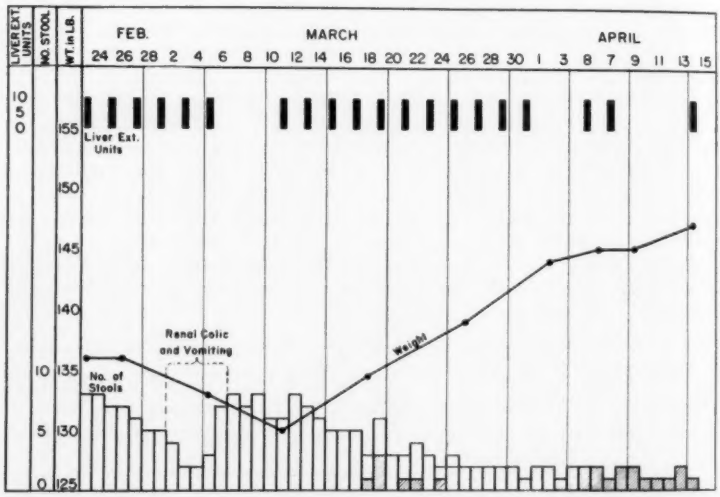

Chart 2 (case 3).—Showing a remission in a case of idiopathic ulcerative colitis coincident with injections of liver extract. A temporary increase in diarrhea was associated with renal colic. In charts 2 and 4 the unshaded columns indicate unformed stools, and the shaded ones indicate formed stools.

the right side, with vomiting for several days. Diarrhea and cramps reappeared and were as severe as previously. Regular opium and liver therapy was resumed on March 11. Within another week the diarrhea and pain had ceased, some of the stools were formed, no blood was discernible grossly in the feces and he was able to be up and about his room. Treatment with opium was stopped, without any increase in the bowel movements. One month after liver therapy was started he was having two normal movements daily, had gained greatly in strength and had increased 9 pounds (4.1 Kg.) in weight in the past two weeks. By the middle of April, seven weeks after the start of the injections of concentrated liver extract, he was ready to leave the hospital. He was feeling well, and his weight had increased from 130 to 147 pounds (59 to 66.7 Kg.),

a total gain of 17 pounds (7.7 Kg.) in five weeks. Proctoscopic examination before dismissal showed a normal-appearing intestinal wall, without a trace of edema or ulceration. The blood count was normal. Roentgen examination after a barium enema showed absence of haustration in the distal portion of the colon.

Comment.—The development of a complete remission in this case paralleled the liver therapy.

CASE 4.—*Chronic ulcerative colitis, with a short remission subsequent to liver therapy.*

History.—The data concerning this patient were made available by Dr. De Witt K. Burnham. Miss V. B., aged 23 years, a saleswoman, entered the hospital on Feb. 22, 1938, complaining of "ulcerative colitis." She had Vincent's stomatitis two years before entry but otherwise had been well. Eight months before entry dysentery developed, and about twenty watery bowel movements occurred daily. The stools contained blood, pus and mucus. She had been confined to bed on an off since then and had not been up at all during the last two months. Severe cramps preceded the passage of stools. No loss of weight had occurred, but her usual weight was only 98 pounds (44.5 Kg.). She had been markedly anemic, but this condition had cleared up. Examination of the stools did not show parasites, and culture gave negative results for dysentery bacilli. The diagnosis of ulcerative colitis was substantiated by a gastrointestinal roentgen study. Treatment with diet, opium and vitamins had failed to improve her condition materially, although there had been as few as seven stools daily on occasion. At entry she was having from four to nine evacuations daily and felt fairly well.

Examination.—Physical examination revealed nothing remarkable. She was afebrile except for an occasional rise of temperature to 99.4 F. The urine was normal. A blood count was normal except for a leukocyte count of 15,200. Two liquid stools did not show amebas but contained much occult blood. Mucus and pus were not noted. Culture of the stools gave negative results for dysentery bacilli. Hinton and Kahn tests of the blood gave negative reactions. A fractional gastric analysis revealed normal acidity. A tuberculin test gave a moderately positive reaction but had given a positive reaction three years previously. A Frei test gave a negative reaction. Proctoscopic examination showed granular ulceration of the whole intestinal mucosa. Smears made of material from the rectal wall showed no amebas. A roentgen study after a barium enema demonstrated that the entire colon was tender, irritable, spastic and "smoothed out." A fine irregularity of the transverse colon was interpreted as probably being due to ulceration.

Treatment and Course.—In addition to her previous treatment she was given a cod liver oil concentrate, calcium gluconate, enemas of salt solution and a course of instillations of carbarsone and a preparation of colloidal kaolin [7] into the lower portion of the bowel. On March 11, two and one-half weeks after entry she was given daily injections of 0.5 cc. of concentrated liver extract [6] for nine consecutive days. She was dismissed from the hospital on March 30, five weeks after entry and only two and one-half weeks after the start of liver extract therapy. She had no liver therapy during the last ten days in the hospital. The diarrhea was unaltered, although her general condition was said to be improved.

7. The preparation used was kaomagma (John Wyeth & Brother, Inc.). Each hundred cubic centimeters contains 20 Gm. of colloidal kaolin and 90 Gm. of aluminum hydroxide gel.

She reentered the hospital for one day on April 4, three and one-half weeks after the first entry. For two weeks she had usually had only three movements daily, and these were well formed and often free from mucus. The abdominal cramps were definitely less severe, and she felt well. Proctoscopic examination at this time showed essentially the same condition as previously except that some areas of the mucosa seemed improved; no new ulcer formation was evident. She returned home. Early in May it was reported that on some days she had only one bowel movement, which was normally formed, and that she was free from abdominal pains. Later in May she was apparently having a relapse as pain and diarrhea had returned. Treatment with vitamin C intravenously was started. No further liver therapy was given, as her remission was not ascribed to the injections of concentrated liver extract given during the middle of March.

Comment.—The beneficial effect of liver therapy is difficult to evaluate in this case as it was given over such a short period. The remission, which became evident about the fourth week after the injections of liver extract were started, appeared at about the same time as in the other cases and may well have been due to the liver extract. The subsequent relapse without further injections of liver extract is in keeping with this assumption.[7a]

CASE 5.—*Low grade ulcerative colitis of long standing, with the first sustained improvement with liver therapy.*

History.—The record of this case was made available by Dr. A. L. Bloomfield. Mr. H. C., a student aged 21 years, first came under observation on Sept. 27, 1937, complaining of diarrhea. He had been in good health until one year before entry, when diarrhea and abdominal pains developed. This condition had been almost constant since then. There had been an average of three to eight poorly formed movements daily which contained blood and mucus. He had maintained his body weight and strength. Proctoscopic examinations repeatedly disclosed ulcerations. The stools never contained amebas, although a positive agglutination reaction for Flexner serum was obtained from a culture of fecal bacteria. Roentgen examination after a barium enema revealed no abnormality. The urine was normal. The blood count showed slight anemia. Kahn and Kline tests for syphilis gave negative reactions. Gastric analysis revealed hyperacidity. He was treated with diet, retention enemas, kaolin, vitamins A, B, C and D, antidysentery serum and streptococcus vaccine. He was reported to have shown some improvement temporarily after serum therapy. When he was first seen by Dr. Bloomfield, results of physical examination were unimportant, although the descending colon was palpable. The urine and blood counts were normal. Two examinations showed blood and pus in addition to formed stools. No amebas were seen. Culture gave negative results for the dysentery group of organisms. Proctoscopic examination revealed the typical picture of superficial chronic ulcerative colitis. Scrapings from the ulcers showed no amebas. A roentgen study after a barium enema showed no evidence of disease of the colon. A course of sulfanilamide treatment given in January 1938 was without benefit. Another course of vaccine therapy was started in February. The diarrhea persisted. The patient kept a daily account of his bowel movements, which showed an average of "forty per week."

7a. Subsequently, while receiving liver extract consistently, this patient became free from symptoms.

Treatment and Course.—On March 15, 1938, injections of concentrated liver extract [6] were started. He received 0.5 cc. three times a week for the first three weeks and 1 cc. three times a week thereafter. On April 6, three weeks later, the diarrhea was not materially altered, but proctoscopic examination showed less edema and ulceration of the intestinal mucosa and some normal-appearing areas. Another proctoscopic examination was performed on May 13, five weeks later and just two months after the start of liver treatment. The intestinal wall was almost free from ulceration and edema but still bled easily if traumatized. The diarrhea had definitely improved during the past three weeks, the number of stools per week being twenty-seven, twenty and twenty-seven, respectively. On some days there had been only two or three movements. Gross blood had disappeared, and the amount of mucus was considerably diminished.

Comment.—This patient seemed definitely improved clinically and by protoscopic examination for the first time in one and one-half years. The improvement was coincident with liver therapy and took place after many other forms of treatment had been tried without benefit.[7b]

CASE 6.—*Long-standing diarrhea, with the recent development of severe ulcerative colitis; two remissions occurring while liver therapy was in progress.*

History.—Mrs. R. A. C., aged 35 years, was seen in consultation with Dr. Ralph Howe on April 5, 1938. He had first seen her the previous November, when she complained of lassitude and diarrhea, and had cared for her since then. Since childhood she had suffered from digestive upsets and occasional looseness of the bowels and had never been robust or strong. She attended the Mayo Clinic fifteen years ago because of these complaints and was told she had mild colitis. One and one-half years ago, while in Pasadena, Calif., she was told that she had amebiasis and was treated with an amebicide (iodoxyquinoline sulfonate). She was not relieved but subsequently had some injections of liver extract and felt much improved. During the first two months under Dr. Howe's care she was hospitalized because of nausea, occasional vomiting, weakness, abdominal cramps, low grade fever and dysentery. The stools were frequent and watery and showed much pus and blood. Amebas were not found in repeated examinations. Culture of the stool and agglutination tests gave negative results for dysentery bacilli. Proctoscopic examination revealed a number of necrotic ulcers of the rectosigmoid region.

Many forms of therapy were tried, including continuous treatment with whole liver extract with iron and vitamin B_1 by mouth and ten injections of ascorbic acid intravenously. Because of her prostration and the development of anemia a blood transfusion was given on Jan. 15, 1938, and the next day treatment with 0.5 cc. of concentrated liver extract [6] was started. Two subsequent injections of this liver extract were given at weekly intervals and another transfusion. Coincident with this liver therapy she improved markedly, the abdominal pains and dysentery ceased, her strength returned and she left the hospital the first of February. During the next six weeks she was in the best of health, "the best in years," and gained 20 pounds (9.1 Kg.) in weight. A proctoscopic examination the middle of March showed only two ulcers, both of which appeared to be healing. During the last part of March all her old symptoms returned,

7b. This patient recovered completely after milk was removed from the diet, and he no longer required liver therapy.

the diarrhea became profuse and the stools contained pus and blood. She reentered the hospital on April 12, suffering from great weakness, nausea, abdominal cramps, dysentery and fever.

Treatment and Course.—She remained in the hospital and received 0.5 cc. of concentrated liver extract [6] three times a week. By the third week she was much improved (chart 3). The diarrhea had practically ceased, the stools were formed and the amount of blood and mucus were greatly diminished. The temperature became normal, and her appetite was good. She returned home on April 27 and received three injections of the concentrated liver extract for the first week and had two injections a week regularly after that. She gained steadily in weight and strength during May, and there was an average of only two stools daily. Only slight traces of blood and mucus occurred during this time. When visited

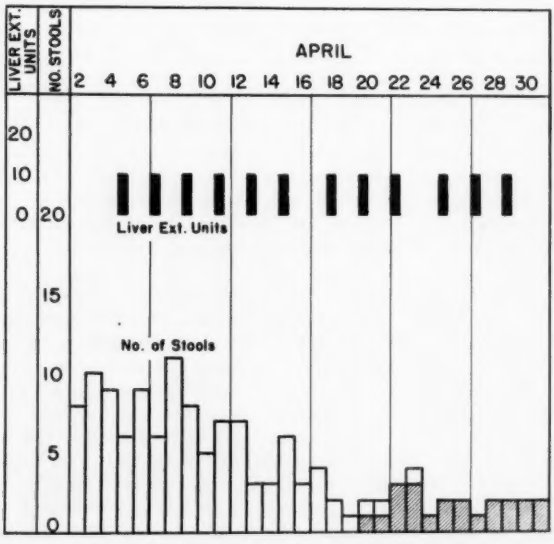

Chart 3 (case 6).—A rapid remission in a case of ulcerative colitis of the septic type, occurring coincident with the parenteral administration of liver extract. The patient had had a similar remission with liver therapy previously but subsequently had a relapse after the treatment was stopped.

at her home on May 23 she appeared well and made no complaint of any intestinal disorder.

Comment.—Excellent remissions occurred twice in this case after the use of liver extract. As no other special therapy was instigated the second time, improvement could hardly be considered independent of injections of liver extract.

CASE 7.—*Extensive ulcerative colitis, with anemia, fever and marked emaciation, progressive for the last year and a half, an excellent remission being coincident with liver therapy.*

History.—Miss E. C., a 20 year old student, was first seen in the hospital on Nov. 4, 1937. She complained of diarrhea. She had a brief attack two years before entry. One year before entry the diarrhea returned, and she had suffered ever since from anorexia, recurrent vomiting, abdominal pains, fever, prostration and amenorrhea. She had eight to fifteen stools daily, which were not formed and contained blood, pus and mucus. She had lost 15 pounds (6.8 Kg.) in weight recently and weighed only 87 pounds (39.5 Kg.) at the time of entry. Many forms of treatment had been tried, but none had helped her.

Examination.—She was thin and pale. The descending colon was readily palpable as a cordlike structure. Four examinations of stools failed to show any amebas. All showed blood and pus. Culture of stool showed Streptococcus viridans, Bacillus proteus and Bacillus coli but no dysentery bacilli. Agglutination tests for typhoid, paratyphoid A and B and Bacillus dysenteriae gave negative results. The urine was normal. A Wassermann test of the blood gave a negative reaction. Repeated blood counts showed hypochromic anemia, with the hemoglobin value varying between 50 and 60 per cent. No leukocytosis occurred despite a slight rise in temperature daily. Two Frei tests with different antigens gave negative results. Proctoscopic examinations revealed an annular constriction about 5 cm. above the anus. The intestinal wall contained chronic and recent ulcers and scar tissue. Smears from the ulcers did not show amebas. A biopsy of the constricting lesion showed subacute suppurative proctitis. Roentgen examination after a barium enema showed narrowing of the colon from rectum to cecum and absence of haustral markings in this area. Five irregularities were noted on the surface of the bowel.

Treatment included the employment of a high caloric and high vitamin diet, brewers' yeast, thiamin, cod liver oil, insulin, iron, sulfanilamide, fever therapy (typhoid vaccine) and blood transfusion, without any benefit. She returned to her home in the country after one month's hospitalization. For four months she constantly suffered from weakness, abdominal pains and diarrhea of varying degree. During January 1938 she had a number of colonic irrigations while under the care of a chiropractor. After this treatment she was much worse, so that during February she was confined to bed and had as many as twenty bowel movements daily. During March she was somewhat improved and was able to be up and about. At this time she was taking "every kind of vitamin except E" by mouth. She had not consulted a doctor in two months.

Course and Treatment.—She was seen by me at the office of Dr. J. C. Drake, near her home, on April 8 and was given 1 cc. of concentrated liver extract [6] intramuscularly. She was having an average of ten stools in twenty-four hours, nearly all at night. They were unformed and usually contained some mucus and blood. Abdominal distress was frequent. Her weight was 92 pounds (41.7 Kg.). During the next two weeks she received three injections a week and thereafter two injections of the concentrated liver extract until May, when she received one injection weekly. The relation of this therapy to the number and the type of the bowel movements and to the body weight is shown graphically in chart 4. Definite improvement was evident by the end of the third week of liver treatment; by the fourth week the diarrhea was greatly reduced, some of the stools were formed and contained no blood, the appetite was good, abdominal pains were much diminished, she had gained in strength and her weight had increased 7 pounds (3.2 Kg.).

Early in May she contracted a severe infection of the upper respiratory tract, with some increase in the intestinal symptoms. Although this infection lasted about two weeks, her general condition continued to improve, so that by the end

of May she weighed 105 pounds (47.6 Kg.) and felt like returning to business college. Also she had had two normal menstrual periods in the last two months, her first in one and one-half years.

Comment.—This girl was prostrated by ulcerative colitis, which was present in a severe and complicated form. Although she has not completely recovered during the seven weeks of intensive parenteral therapy with liver extract, her improvement has been so marked that a causal relation between it and the treatment can hardly be doubted.[7c]

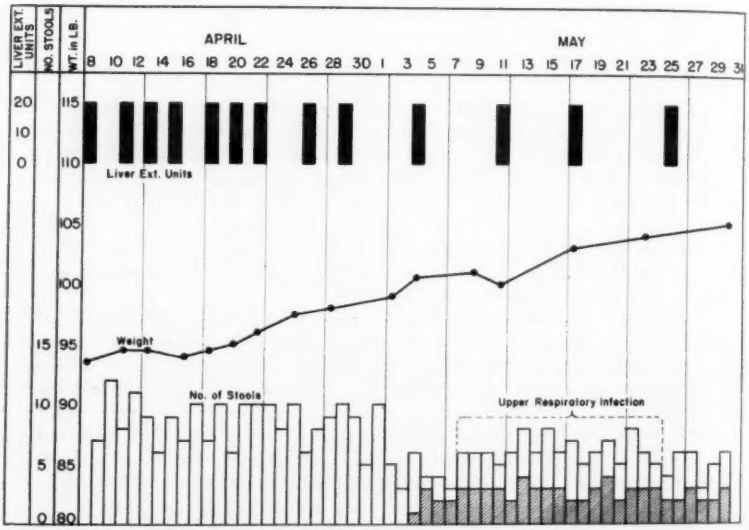

Chart 4 (case 7).—Showing the reduction of diarrhea and the gain in weight in a case of severe ulcerative colitis of over two years' duration. Improvement was coincident with parenteral liver therapy. A slight increase in diarrhea occurred during an infection of the upper respiratory tract. The patient is still under treatment.

CASE 8.—*Chronic diarrhea with recurrent attacks of colitis; ulceration not proved; improvement with liver therapy.*

History.—Mrs. P. S., a secretary aged 23 years, was first examined on June 15, 1937, when she had no complaints. Her appendix had been removed ten years previously. There had been some soreness in the region of the operative scar ever since. During the last two years she had suffered three attacks of severe abdominal pains and tenesmus, said to be due to an ovarian disorder. For the past year there had been two to four bowel movements daily. The stools were often soft and occasionally were accompanied by mucus. She had not lost weight.

7c. With continued liver therapy she became free from symptoms and returned to school.

Physical examination revealed no abnormality except moderate tenderness in the left lumbar region and the right side of the abdomen. Pelvic examination revealed no abnormality. The urine was normal. The hemoglobin value was 74 per cent. The blood sedimentation rate was 8 mm. in sixty minutes. A Kahn test of the blood gave a negative reaction. Pyelograms outlined a normal-appearing urinary tract.

She had had continuous intestinal disorder since Nov. 1, 1937, except for a respite during February 1938. She complained of recurrent abdominal cramps with soreness, distention, tenesmus, loose stools, that were poorly formed and often contained much mucus, and loss of strength. At times the lower portion of the abdomen was acutely tender. A low grade fever was present intermittently. Examination of the stool showed no ova or parasites. Roentgenograms of the gastrointestinal tract showed an irritable condition of the duodenal bulb, a tender, movable cecum that was normally outlined and a spastic area in the descending colon, suggesting the presence of ulcers. The sigmoid flexure was tender. There was no evidence roentgenologically of ileitis. In March she had to stop work because the symptoms had become so pronounced. At this time the blood count and sedimentation rate were normal. A tuberculin test (1:25,000) gave a negative reaction. Proctoscopic examination revealed no evidence of inflammation or ulceration in the lower 15 cm. of bowel. She was put to bed at home.

Treatment and Course.—She was given a high caloric and nonresidual diet, a hemicellulose preparation[8] and capsules containing vitamins B_1 and B_2 complex,[9] and on March 8 she received her first injection of 0.5 cc. of concentrated liver extract.[6] These injections were repeated on March 10, 12, 14, 18, 22 and 29. She received three injections in April and two in May of 0.5 cc. each, except for a dose of 1cc. on April 15. The third week after the injections of liver extract were started she began to improve, and by the fourth week she was free from abdominal cramps and tenesmus and for the first time in almost two years was having only one well formed stool daily. All therapy except the use of liver extract was stopped. She was able to return to work the latter part of April and has been free from symptoms since, except for some gas and slight soreness in the region of the cecum. On May 7 an alcohol test meal showed normal gastric acidity.

Comment.—The findings in this case were typical of idiopathic ulcerative colitis in the stage before ulceration becomes pronounced. A remission took place during parenteral therapy with liver extract and has been maintained for two months.

COMMENT

The histories of these 8 patients with idiopathic ulcerative colitis show that a remission took place in each case about the same interval after treatment with injections of liver extract was started. Although remissions naturally occur during the course of the disease and the num-

8. The preparation used was metamucil, obtained from Plantago ovata.

9. The preparation used was betalin compound (Lilly). According to the manufacturer, each capsule contains "150 International units vitamin B_1 (1.0 mg. Thiamin Chloride) and 40 Sherman units vitamin B_2 (G) with other factors of vitamin B_2 Complex from Liver-Stomach Concentrate."

ber of patients treated is small, such a uniformity of results could hardly be entirely coincidental, particularly as these patients had never shown sustained improvement with any other form of therapy. Most of them showed some evidence of improvement by the third or fourth week of treatment, and definite improvement was invariably manifest by the second month. Those with many ulcers and but slight physical disability were slower in showing an alleviation of symptoms which could be positively recognized. Certain symptoms are worthy of special attention.

The diarrhea was as a rule definitely diminished by the end of the third week. Usually the number of bowel evacuations was at least halved. One patient (case 3) showed rapid improvement, diarrhea ceasing at the end of the first week of treatment, only to recur coincident with the development of renal colic. In case 5 the diarrhea was not profuse, and well over a month passed before a definite reduction in the number of stools could be noted. Tincture of opium and camphorated tincture of opium were helpful adjuncts in reducing the diarrhea but never in themselves completely controlled it. Nervousness, excitement, intercurrent infections and other factors disturbing to the patient produced temporary increases in bowel movements, particularly early in the course of therapy. This is nicely illustrated in cases 3 and 7 (charts 2 and 4). Diarrhea ceased altogether during the second month, except in case 6, the number of movements ranging between one and three daily. If adequate maintenance treatment with liver extract was not continued, recurrence of the diarrhea occurred from two to four weeks after it had been stopped. In cases 2, 4 and 6 such relapses developed.

If the patient was not having any formed stools, some of them became formed by the end of the first month of treatment with injections of liver extract. Liquid defecation ceased entirely during the second month (charts 2 to 4). Gross pus commonly disappeared from the stool within one or two weeks. Gross blood and mucus were more persistent but were absent or occurred only in traces by the end of the second month of adequate therapy. They tended to reappear promptly if the diarrhea increased. The cramps and tenesmus improved as the diarrhea subsided and usually disappeared with the cessation of the expulsion of liquid feces and gas. When fever was present and closely observed it tended to subside within five to ten days. This was particularly noticeable in cases 2 and 6, in which the temperature reached 102 F. before the liver therapy was started.

When the loss of weight was marked, improvement in nutrition and gain in weight were often striking. The curves in charts 1, 2 and 4 show this graphically. The gain was commonly apparent by the third week of liver therapy and commenced even before diarrhea ceased. In 3 cases

(cases 4, 5 and 8) the loss of weight was not a feature of the illness. Improvement in the general condition was highly gratifying but was what would be expected in any one recovering from a prolonged siege of dysentery. In half the cases the patient has already returned to his normal mode of living after a prolonged period of disability.

Direct objective evidence of improvement in the colitis is furnished by follow-up proctoscopic examinations in 6 of 7 cases in which ulceration was observed before liver therapy was started. In 1 case the intestinal mucosa appeared normal two months after therapy was started. In 2 cases (cases 1 and 2) the intestinal wall was normal except for one or two small hemorrhagic areas four and eight months, respectively, later. In the 3 remaining cases (cases 4, 5 and 6) ulcerations were still present six weeks later, but pronounced improvement was evident in 2 and slight but definite involvement in 1. The last-mentioned patient (case 4) had received no maintenance therapy after the original nine consecutive days of treatment. It may be concluded from these observations that healing of the intestinal wall may be evident as early as the second month and may become complete subsequently. Further follow-up proctoscopic examinations are of course necessary to clarify the rapidity and extent to which healing of the pathologic process may take place. As structural changes in the bowel vary so much from case to case, naturally the rate of healing will vary in proportion to their extent and chronicity. Follow-up roentgen studies have been carried out in only 2 instances, cases 1 and 2. No definite changes in the intestinal outline have occurred, but it could hardly be expected that alterations in the contour of the intestinal wall due to fibrosis would be likely.

The exact amount of liver extract which must be injected to induce a remission in idiopathic ulcerative colitis cannot yet be stated. In the 8 cases described, excessively large doses were given as a rule, simply in the hope of obtaining some degree of therapeutic success. If in case 2 the temporary improvement which occurred in August 1937 can be attributed to the liver extract which had been injected, the response occurred after the administration of approximately 30 units in one week. A similar amount apparently initiated the first remission in case 6. In both these cases and in case 4 only a brief course of liver therapy was given; although each patient improved temporarily, a relapse subsequently took place. The other courses of treatment were practically continuous, ranging from the injection of 10 or more units weekly to the administration of 10 to 20 units three times a week in the first weeks. The correct maintenance dose is also difficult to calculate except by the method of trial and error. Judging from the record in case 2, it may need to be as much as 20 units every seven to fourteen days. In cases 1 and 8 apparently as little as 10 units was needed every two

weeks. As clinically and pathologically idiopathic ulcerative colitis varies greatly in its severity, it would not be surprising to find that the dose of a successful therapeutic agent would also have to be variable. Practically, a patient should receive not only enough of this agent to make him well but also enough thereafter to keep him free from symptoms. At present this will have to be determined for each patient.

The concentrated liver extract used was reticulogen [6] in all cases except for brief periods in cases 1 and 2. A nonconcentrated preparation of liver [5] was used in case 1 in alternate doses with the concentrated extract and in the first course of injections given in case 2. Another brand of concentrated liver extract (Lederle) was used on two occasions in the early treatment in case 2 last winter. The only known advantage of reticulogen over the other brands of liver extract is its great concentration, making possible the administration of a highly potent substance in small doses. It seems possible that the addition of vitamin B_1 to reticulogen is an important factor, as it had not been added to the two other liver preparations used; but they seemed to be effective as far as may be judged from the available data.

In the management of idiopathic ulcerative colitis a trial of parenteral liver therapy should consist of the intramuscular injection of 10 units of liver extract three times a week for the first month, then 20 units a week for the second month and a maintenance dose of 20 units every two weeks thereafter. In exceptional instances the maintenance dose may have to be increased to 20 units every seven to ten days (see case 2 and chart 1). It may also be reduced to 10 units once in two to four weeks if the disease is mild.

A study of these 8 cases of idiopathic ulcerative colitis in which injections of liver extract were given suggests that liver contains some substance which promotes healing of the disease process in the bowel. The nature of this apparently beneficial factor is unknown. Vitamin B_1 has been added to reticulogen in the proportion of 1,000 international units per cubic centimeter, and liver extract already contains some vitamin B_1. It seems highly improbable that lack of this vitamin alone can cause ulcerative colitis, as in the vitamin B_1 deficiency beriberi ulceration of the bowel does not occur. The same argument seems to hold good for the antipellagra (P-P) factor of the vitamin B complex, which is contained in liver. Although diarrhea is common in pellagra, colonic ulcers do not commonly occur except in far advanced or terminal conditions. The factor potent against pernicious anemia (fraction G of Cohn) contained in liver could hardly play a primary role, as ulceration of the bowel is not a symptom of pernicious anemia. However, this type of anemia may occur as a complication of nonspecific ulcerative colitis.[3] No exact analysis of reticulogen is as yet available, but it seems

likely that liver contains some as yet unknown substance which promotes healing of the bowel together with restoration of normal function and relief of symptoms of a disease which has heretofore withstood all therapeutic efforts to alter its chronicity and often fatal outcome. It must be emphasized that the reported findings in no way suggest a cure for ulcerative colitis, but they do suggest that a remission may be induced and maintained by the regular administration of liver extract by intramuscular injection.

CONCLUSIONS

Definite remissions have occurred in 8 cases of idiopathic ulcerative colitis subsequent to the intramuscular injection of concentrated liver extract.

Relapses have developed after the administration of liver extract has been stopped and have cleared up when liver therapy has been resumed.

It is the clinical impression of the physicians who have observed 7 of these 8 patients that the remissions were caused by the treatment with liver extract and were not coincidental. The eighth patient was insufficiently studied.

The administration of liver extract parenterally can in no way be considered a cure for idiopathic ulcerative colitis.

It is probable that the substance contained in liver which seems to exert a beneficial effect on the course of ulcerative colitis is one at present unknown and is not identical with vitamin B_1 or B_2 or fraction G of Cohn.

VENTRICULAR ASYNCHRONISM IN BUNDLE BRANCH BLOCK

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The symptoms arising from damage of the branches of the bundle of His have been studied for years by many investigators with the aim of ascertaining (*a*) if there exists a complete block (*b*) and if so which is the branch blocked. Most of the study has been devoted to the electrocardiographic changes, and though these changes are important for the diagnosis of bundle branch block, considerable difference of opinion has developed among investigators as to their value in determining the branch involved.

Studying this problem experimentally and clinically, we have been able to find graphic signs of the ventricular asynchronism which is the fatal consequence of bundle branch block. Marked asynchronism in the contraction of the ventricles indicates with certainty that bundle branch block exists. Furthermore, it enables one to determine definitely which ventricle contracts first.

VENTRICULAR ASYNCHRONISM IN EXPERIMENTAL BUNDLE BRANCH BLOCK

Although slight asynchronism has been found normally by Katz,[1] the onset of contraction of the ventricles may be considered to be practically synchronous.

This synchronism is due to the speed with which the impulse spreads through the branches of the bundle of His, exciting the two ventricles at the same time. If experimentally one of the bundle branches is crushed, marked ventricular asynchronism results. This was investi-

From the Instituto de Fisiología de la Facultad de Ciencias Médicas, Universidad Nacional de Buenos Aires.

1. Katz, L. N.: Asynchronism of the Right and Left Ventricular Contraction and the Independent Variations in Their Duration, Am. J. Physiol. **72**:655, 1925.

gated by Eppinger and Rothberger,[2] who observed—in only one experiment for each bundle branch—that after the left branch was cut, the onset of the pulse wave of the pulmonary artery preceded the onset of the wave of the aortic pulse by 0.02 to 0.03 second and vice versa after section of the right branch.

After cutting the right branch of the bundle of His in dogs and by means of optical registration of the mechanical events of the ventricular activity, we [3] have been able to demonstrate the following points:

(*a*) Asynchronism in the onset of contraction of the two ventricles, the contraction of the left ventricle preceding that of the right by 0.04 second (figs. 1 and 2)

(*b*) Asynchronism in the onset of the ejection of blood from the two ventricles, the aortic pulse preceding the pulmonary pulse by 0.01 to 0.04 second (fig. 3)

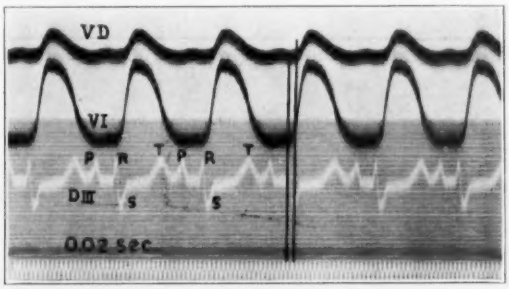

Fig. 1.—Synchronous records of right (*VD*) and of left (*VI*) intraventricular pressure (electrocardiogram, lead III; time, 0.02 second) for a dog after the right bundle branch had been cut. The rise of pressure in the left ventricle precedes that in the right by about 0.04 second.

(*c*) Asynchronism in the closure of the semilunar valves of the aorta and those of the pulmonary artery, the aortic second sound preceding the pulmonic second sound by about 0.06 second

(*d*) Prolongation and, generally, reduplication of the first heart sound

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2. Eppinger, H., and Rothberger, C. J.: Ueber die Sukzession der Kontraktion der beiden Herzkammern, insbesondere nach einseitiger Blockierung der Erregungsüberleitung, Zentralbl. f. Physiol. **24**:1055, 1910.

3. Braun-Menendez, E., and Solari, L. A.: Asincronismo ventricular por sección de las ramas del haz de His: I. Sección de la rama derecha, Rev. Soc. argent. de biol. **12**:331, 1936; abstracted, Compt. rend. Soc. de biol. **124**:251, 1937.

(*e*) Prolongation of the interval between the aortic incisura and the summit of the v wave of the venous pulse.

After experimental section of the left branch we [4] also observed the ventricular asynchronism (in this case the contraction of the right

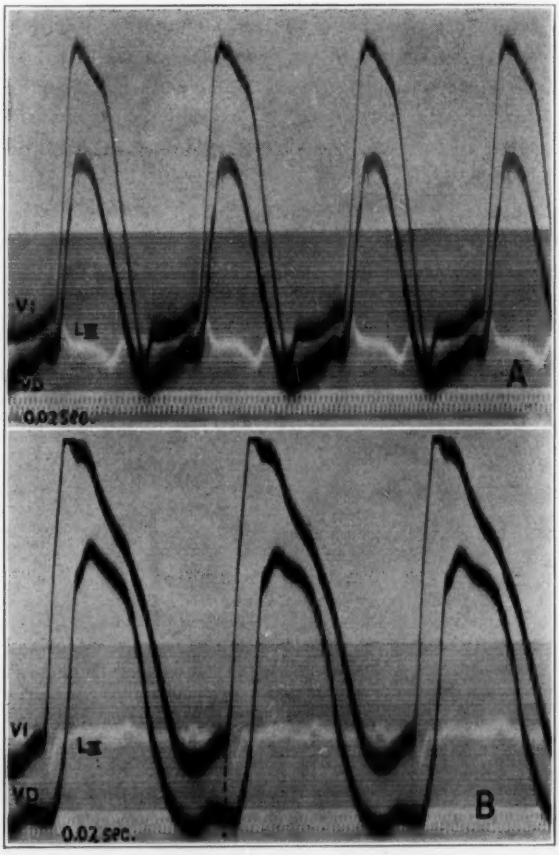

Fig. 2.—Synchronous records of the contraction in the left ventricle (*VI*) and in the right ventricle (*VD*), the cardiograms being made before (*A*) and after (B) the right bundle branch of the dog was cut (electrocardiogram, lead III; time, 0.02 second). Before section the ventricles contracted synchronously; after section the left ventricle contracted 0.04 second before the right.

4. Braun-Menendez, E., and Solari, L. A.: Asincronismo ventricular por sección de las ramas del haz de His: II. Sección de la rama izquierda, Rev. Soc. argent. de biol. **13**:33, 1937; abstracted, Compt. rend. Soc. de biol. **125**:531, 1937.

ventricle preceded that of the left), although it was not so evident as in the case of section of the right branch.

It is clear, then, that bundle branch block is followed by marked ventricular asynchronism, which no doubt in many ways influences the mechanical action of the heart.

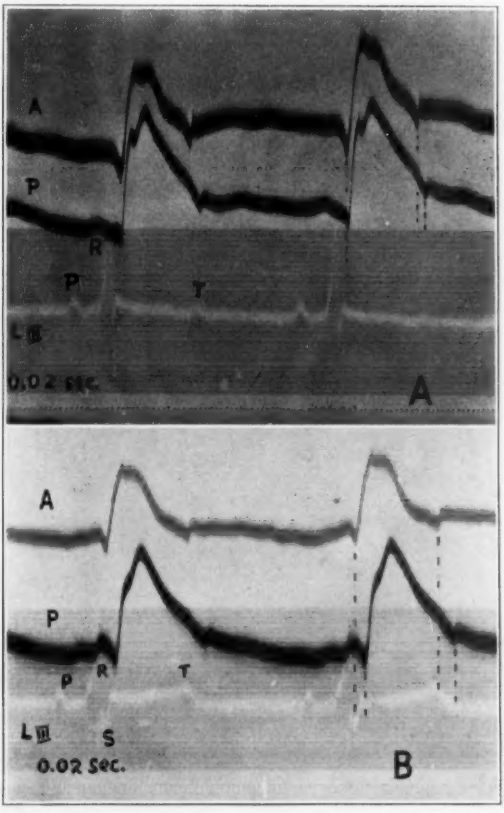

Fig. 3.—Simultaneous records of the aortic and of the pulmonary pulse before (*A*) and after (*B*) the right branch of the bundle of His of the dog was cut (electrocardiogram, lead III; time, 0.02 second). Before section the rise of the aortic and that of the pulmonary pulse were synchronous, and the aortic incisura preceded the pulmonary incisura by about 0.03 second. After section of the right branch the rise of the aortic pulse preceded that of the pulmonary by 0.04 second, and the aortic incisura preceded the incisura of the pulmonary pulse by 0.06 second.

CLINICAL DEMONSTRATION OF VENTRICULAR ASYNCHRONISM

The electrocardiogram has heretofore been almost exclusively the only means employed for the diagnosis of bundle branch block. With this method Eppinger and Stoerk [5] diagnosed bundle branch block for the first time in man and determined which branch was involved. But after that the observation of many other clinical cases led authors to absolute disagreement. Some [6] observed (classic criterion) that when

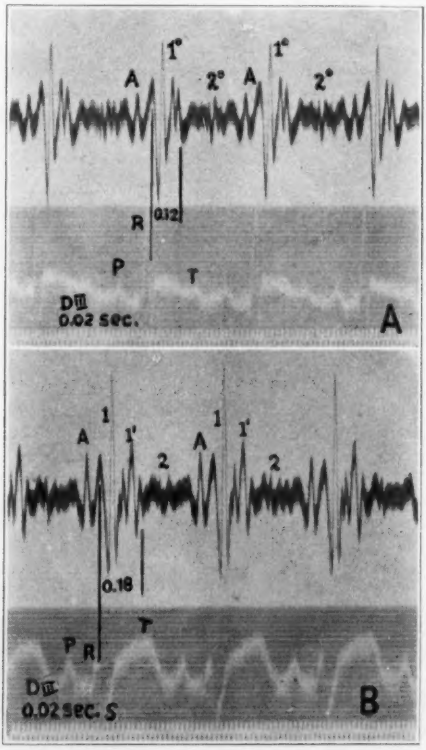

Fig. 4.—Heart sounds explored by way of the esophagus before and after section of the right branch of the bundle of His of the dog (electrocardiogram, lead III; time, 0.02 second). After section of the right branch the first heart sound was prolonged and reduplicated.

5. Eppinger, H., and Stoerk, O.: Zur Klinik des Elektrokardiogramms, Ztschr. f. klin. Med. **71**:157, 1910.

6. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, Shaw & Sons, 1925. Mahaim, I.: Les maladies organiques du faisceau de His-Tawara, Paris, Masson & Cie, 1931. Rothberger, C. J.: Zur Diagnose des Schenckelblockes, Ztschr. f. klin. Med. **123**:460, 1933.

the right bundle branch is blocked the electrocardiogram shows a tall, broad R wave in lead I and a deep S wave in lead III, the final T wave being in the reverse direction to the main initial wave in each lead. When left bundle branch block is present the electrocardiogram shows a deep S wave in lead I and a tall R wave in lead III.

In recent years some authors [7] have given convincing proof that the nomenclature of bundle branch block is the opposite of that just mentioned and that what has hitherto been called right bundle branch block is really left bundle branch block and vice versa.

Finally, according to Katz and his collaborators,[8] the electrocardiogram by itself is unable to give certain proof of the localization of bundle branch block.

In conclusion, although the electrocardiogram may give information as to the existence of bundle branch block, as Katz has pointed out: "It would be unjustified to attempt to localize the site of . . . bundle branch block from the direction of the major initial complex in the three leads of the electrocardiograms."

But there is a means of diagnosing bundle branch block with certainty and of localizing the site of injury; this is the verification of the

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7. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, Arch. Int. Med. **25**:146 (Feb.) 1920. Oppenheimer, B., and Pardee, H.: The Site of the Cardiac Lesion in Two Instances of Intraventricular Heart Block, Proc. Soc. Exper. Biol. & Med. **17**:177, 1920. Barker, P. S.; Macleod, A. G., and Alexander, J.: The Excitatory Process Observed in the Exposed Human Heart, Am. Heart J. **5**:720, 1930. Wilson, F. N.; Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, ibid. **7**: 305, 1931. Marvin, H. M., and Oughterson, A. W.: The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricles, ibid. **7**:471, 1932. Oppenheimer, E. T., and Oppenheimer B. S.: Right and Left Bundle-Branch Block in the Human Heart, Verhandl. internat. Kong. Physiol. **14**:198, 1932; Arch. di sc. biol. **18**:277, 1933. Lundy, C. J., and Bacon, C. M.: Premature Left Ventricular Beats from Electrical Stimulation of the Exposed Human Heart, Arch. Int. Med. **52**:30 (July) 1933. Nichol, A. N.: The Interpretation of Lead Inversion in Bundle-Branch Block, Am. Heart J. **9**:72, 1933. Wolferth, C. C., and Margolies, A.: Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block: Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, ibid. **10**:425, 1935. Brown, W. H.: A Study of the Esophageal Lead in Clinical Electrocardiography: I. The Application of the Esophageal Lead to the Human Subject with Observations on the Ta-Wave, Extrasystoles and Bundle-Branch Block, ibid. **12**:1, 1936.

8. (*a*) Katz, L. N., and Ackerman, W.: Reversal in Direction of the QRS Complex of Experimental Right Bundle-Branch Block with Change in the Heart's Position, Am. Heart J. **8**:490, 1933. (*b*) Katz, L. N.; Landt, H., and Bohning, A.: The Delay in the Onset of the Left Ventricle in Bundle-Branch Block, ibid. **10**: 68, 1935.

ventricular asynchronism—its fatal consequence—by means of adequate registration of the mechanical cardiac events.

COMMENT

If it were possible to determine directly in man the onset of contraction in the two ventricles, the verification of ventricular asynchronism would be easy. But as this is not yet possible, it was found necessary to record optically and simultaneously some of the mechanical events due to the activity of both ventricles.[9]

The optical tracings of the apex beat, the heart sounds, the central arterial pulse and the venous pulse in man when superimposed keep, under normal conditions, the time relations shown in figure 5.

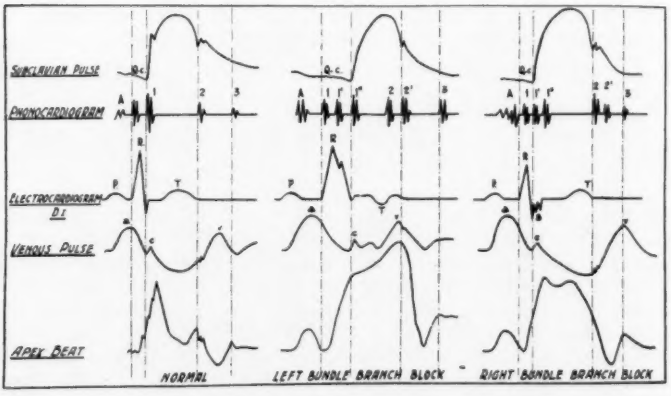

Fig. 5.—Superimposed curves for the subclavian pulse, heart sounds, electrocardiogram, venous pulse and apex beat to show the time relations of these tracings under normal conditions, with left bundle branch block and with right bundle branch block.

As will be pointed out later, some of the events have especial significance. The first sound begins synchronously with the summit of the R wave in the electrocardiogram, and the second sound, which is due to the simultaneous closure of the aortic and of the pulmonary semilunar valves, begins synchronously with the bottom of the incisura of the

9. Battro, A.: Braun-Menendez, E., and Orias, O.: Asincronismo de la contracción ventricular en el bloqueo de rama; su demonstración mediante el registro óptico de los fenómenos mecánicos de la actividad cardíaca. Rev. argent. de cardiol. **3**:325, 1936.

central arterial pulse. There is an interval between the rise of the R wave of the electrocardiogram and that of the central arterial pulse of 0.06 to 0.12 second.

It must be pointed out that in the tracing for the venous pulse, which follows the right intra-auricular changes in pressure, the second sound is represented by a notch which interrupts the rise of the v wave; the summit of the v wave indicates the moment when the tricuspid valve opens, and the decending limb of the v wave indicates the phase of rapid inflow. This phase is also represented in the curve of the apex beat (which follows the movements of the left ventricle) as a rapid early diastolic rise. Because of the delay of the venous pulse waves in relation to those of the apex beat, the summit of this early diastolic rise is coincident with the last portion of the descending limb of the v wave, which is the moment when normally the third heart sound is recorded.

As we [3, 4] have shown experimentally, two aspects may be considered in the ventricular asynchronism which follows section of one of the bundle branches: (1) asynchronism of the onset of contraction of the two ventricles and (2) asynchronism of the end of systole in the two ventricles. The verification of the existence of marked asynchronism of the onset of contraction or of the end of systole gives evidence of the existence of bundle branch block.

The characteristic signs of ventricular asynchronism at the onset of systole that may be observed in man by optical recording of the mechanical events of cardiac activity are as follows:

(*a*) The subdivision and prolongation of the first heart sound. Castex,[10] King,[11] and King and McEachern [12] found by auscultation in many cases of bundle branch block a reduplication of the first sound that Wolferth and Margolies [13] recorded. We [9] found that actually three groups of vibrations are to be distinguished (figs. 6 to 8).

Under normal conditions the first heart sound is formed by two principal groups of vibrations, one of them corresponding to the

10. Castex, M.: Sur le dédoublement et le rédoublement du premièr bruit du coeur, Arch. d. mal. du cœur **16**:401, 1923.

11. King, J. T.: The Clinical Recognition and Physical Signs of Bundle-Branch Block, Am. Heart J. **3**:505, 1928.

12. King, J. T., and McEachern, D.: The Nature of the Physical Signs of Bundle-Branch Block, Am. J. M. Sc. **183**:445, 1932.

13. Wolferth, C. C., and Margolies, A.: (*a*) The Various Types of Extra Heart Sounds, M. Clin. North America **14**:897, 1931; (*b*) Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block; Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, Am. Heart J. **10**:425. 1935.

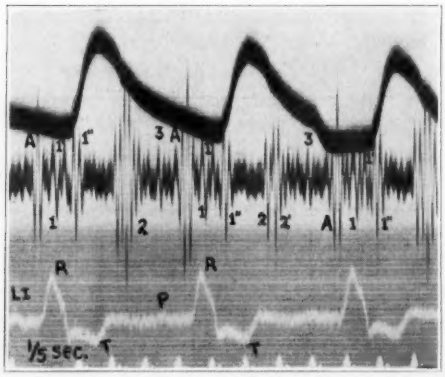

Fig. 6.—Optically recorded subclavian pulse, heart sounds and electrocardiogram (lead I) in a case of the so-called common type of bundle branch block (time, 0.2 second). The record of the heart sounds shows a loud auricular sound, a first sound composed of three groups of vibrations, a reduplicated second sound and a third heart sound. The interval between the rise of the R wave and that of the subclavian pulse is abnormally prolonged (Q-c, 0.16 second). This proved to be a case of left bundle branch block.

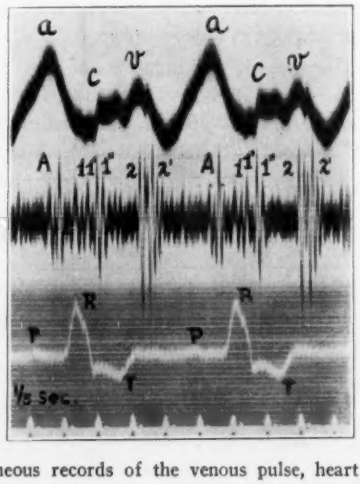

Fig. 7.—Simultaneous records of the venous pulse, heart sounds and electrocardiogram in a case of left bundle branch block. The phlebogram shows a typical change of contour. A notch synchronous with the second component of the reduplicated second sound is seen in the descending limb of the v wave.

isometric contraction phase and the other to the ejection phase. If ventricular asynchronism of more than 0.04 second is present, the second group of vibrations of the sound of one of the ventricles is added to the first group of the other ventricle, and there appear, consequently, three groups of vibrations. The three groups are not always clearly seen, as their demonstration depends on various other factors (e. g., area of registration and presence of postauricular vibrations).

(*b*) The other sign indicative of asynchronism at the onset of contraction of the two ventricles is the prolonged interval between the rise of the R wave and that of the central arterial pulse.[14] The value of this sign is relative, as it depends on many other factors. According to Katz, Landt and Bohning,[8b] an interval of less than 0.14 second discards the possibility of left bundle branch block, and an interval of

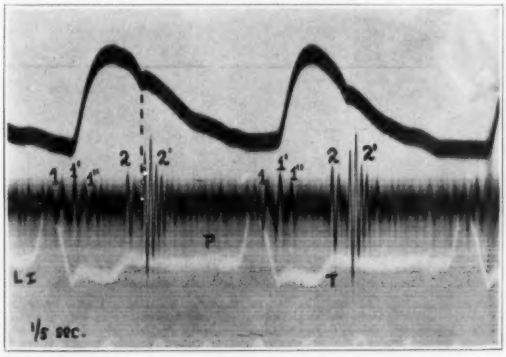

Fig. 8.—Optically recorded subclavian pulse, heart sounds and electrocardiogram (lead I) in a case of left bundle branch block. The second sound is reduplicated, and its first component precedes the incisura.

more than 0.18 second is probably good evidence of its presence (fig. 9).

The most important signs for the diagnosis of bundle branch block are those indicating asynchronism of the end of systole or of the beginning of diastole. These may be obtained in man by the simultaneous record of the heart sounds and central arterial pulse and of the venous pulse and apex beat. These will be analyzed separately:

(*a*) Central arterial pulse and heart sounds. Under normal conditions the second sound is synchronous with the bottom of the incisura of the central arterial pulse or precedes it at most by 0.01 to 0.02 second. The incisura is due to the closure of the aortic semilunar valves, and

14. Nichol, A. N.: The Interpretation of Lead Inversion in Bundle-Branch Block, Am. Heart J. **9**:72, 1933. Wolferth and Margolies,[13b] Katz, Landt and Bohning.[8b]

as these close more or less synchronously with the pulmonary valves, the second sound is single. When the two sets of semilunar valves close asynchronously (as in cases of experimental bundle branch block), the second sound may be reduplicated. By the simultaneous registration of this reduplicated second sound and of the central arterial pulse, sure information may be obtained as to which is the ventricle that first ends its contraction: If the second component of the reduplicated second sound coincides with the incisura of the central arterial pulse and if the first component begins more than 0.05 second before the end of the incisura (figs. 9 and 10), the pulmonary valves close before the aortic valves, and it may be asserted that the ventricular asynchronism present is due to left bundle branch block.[15]

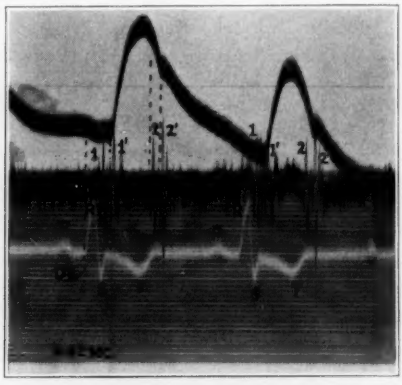

Fig. 9.—Optically recorded subclavian pulse, heart sounds and electrocardiogram (lead II) in a case of left bundle branch block. The second sound is reduplicated, and its first component precedes the incisura.

(*b*) Curves for the venous pulse and for the apex beat. These curves give information as to the moment of the phase of rapid inflow in the two ventricles: The venous pulse follows the right ventricular events, and the curve for the apex beat represents the left ventricular events. The descending limb of the v wave of the venous pulse represents the phase of rapid inflow in the right ventricle; the early diastolic rise of the curve for the apex beat (or the third heart sound when present) represents the phase of rapid inflow in the left ventricle. Under normal conditions the end of the early diastolic rise of the portion of the curve for the apex beat and the third heart sound coincide with the last portion of the descending limb of the v wave. If this early

15. Wolferth and Margolies.[13b] Battro, Braun-Menendez and Orias.[9]

diastolic rise anticipates and coincides with the summit of the v wave, it may be asserted that the onset of relaxation of the left ventricle has preceded that of the right, and therefore right bundle branch block is present (figs. 11 and 12). On the other hand, when the end of the early diastolic rise of the curve for the apex beat (and the third heart sound) follows the end of the descending limb of the v wave of the venous pulse, it may be asserted that the ventricular asynchronism present is due to left bundle branch block (fig. 13).

(*c*) In the curve for the venous pulse, apart from the time relations with the curve for the apex beat just mentioned, a significant change in contour, of great importance for the establishment of the diagnosis of ventricular asynchronism, is to be observed (fig. 14). In

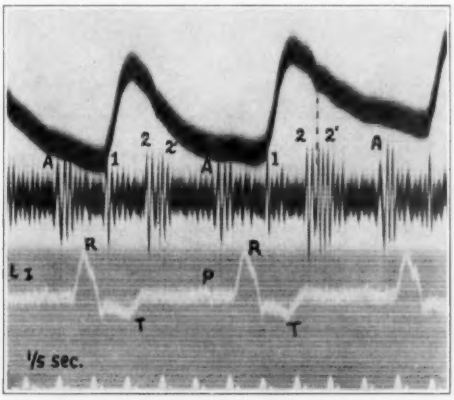

Fig. 10.—Optically recorded subclavian pulse, heart sounds and electrocardiogram (lead I) in a case of left bundle branch block. The second sound is reduplicated, and its first component precedes the incisura.

the curve for the optically recorded venous pulse the ascending limb of the v wave is interrupted by a small notch synchronous with the second heart sound; this is the second aortic sound, which is transmitted from the aorta to the jugular vein through the vena cava, or, in all probability, directly from the carotid or the subclavian artery to the jugular vein. With left bundle branch block these vibrations are to be seen in the summit or early drop of the v wave, owing to the delay in the closure of the aortic semilunar valves (figs. 7 and 13). On the contrary, when right bundle branch block is present and the left ventricle contracts before the right, the notch representing the vibrations of the aortic second sound is anticipated, and the interval between this notch and the summit of the v wave is prolonged (more than 0.13 second, maximal duration of the phase of normal isometric relaxation; figs. 11 and 12).

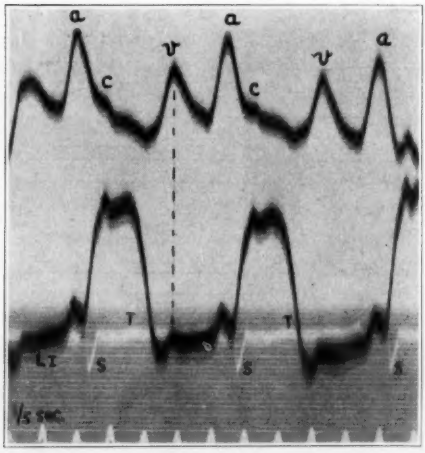

Fig. 11.—Simultaneously recorded venous pulse, apex beat and electrocardiogram (lead I) in a case of right bundle branch block (time, 0.2 second). The early diastolic rise of the curve for the apex beat precedes the drop of the v wave of the phlebogram.

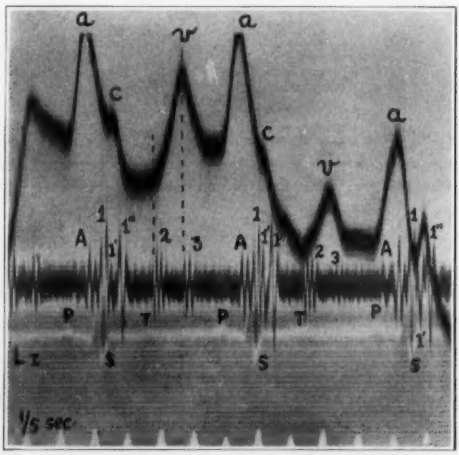

Fig. 12.—Simultaneously recorded venous pulse, heart sounds and electrocardiogram (lead I) in a case of right bundle branch block (time, 0.2 second). The interval between the notch in the curve for the venous pulse, which is synchronous with the second heart sound, and the summit of the v wave is prolonged. The third heard sound coincides with the summit of the v wave (as would be the case for the opening snap in a mitral stenosis).

These are the most important signs for the diagnosis of ventricular asynchronism. An auricular sound may be observed, and it has pathologic significance. When the heart rate is rapid a gallop rhythm may

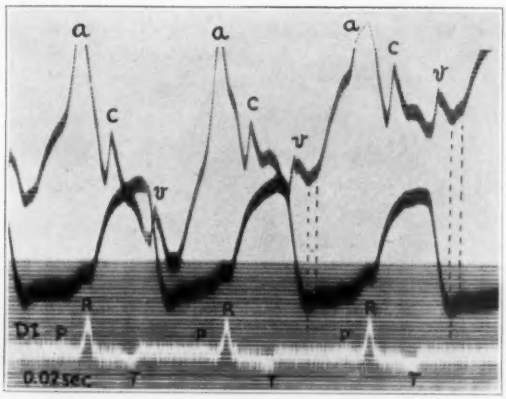

Fig. 13.—Optically recorded venous pulse, apex beat and electrocardiogram (lead I) in a case of left bundle branch block, showing the change of contour of the phlebogram and its time relations with the curve for the apex beat. The descending limb of the v wave precedes the early diastolic rise of the curve for the apex beat (time, 0.02 second).

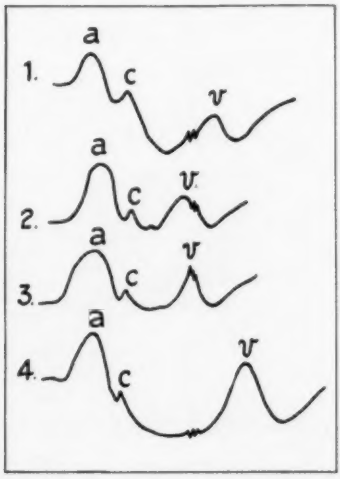

Fig. 14.—The contour of the tracing for the venous pulse (*1*) under normal conditions, (*2* and *3*) with left bundle branch block and (*4*) with right bundle branch block.

ensue; if it is slow, the sequence of the auricular and the first heart sound may be interpreted by auscultation as showing a reduplicated first heart sound.

We may briefly state that by optically recording for a patient the apex beat, the venous pulse, the heart sounds and the subclavian or

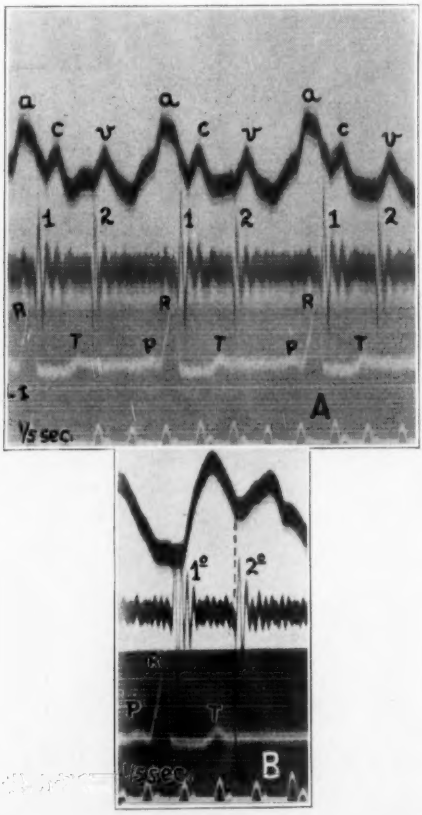

Fig. 15.—Optical records (*A*) of the venous pulse together with the heart sounds and (*B*) of the subclavian pulse together with the heart sounds, showing no sign of asynchronous action of the two ventricles in a case of so-called bundle branch block with a short PR interval (electrocardiogram, lead I; time 0.2 second).

carotid pulse simultaneously, it is possible to recognize: (1) the existence of ventricular asynchronism and hence of bundle branch block, and (2) the localization of the bundle branch block by determining which ventricle contracts first.

Applying these procedures, a study was made [9] of 20 patients whose electrocardiographic records were considered as characteristic of so-called bundle branch block. In 17 cases there were electrocardiographic records of the so-called common type of bundle branch block (right bundle branch block, according to the old nomenclature). In 15 of these cases

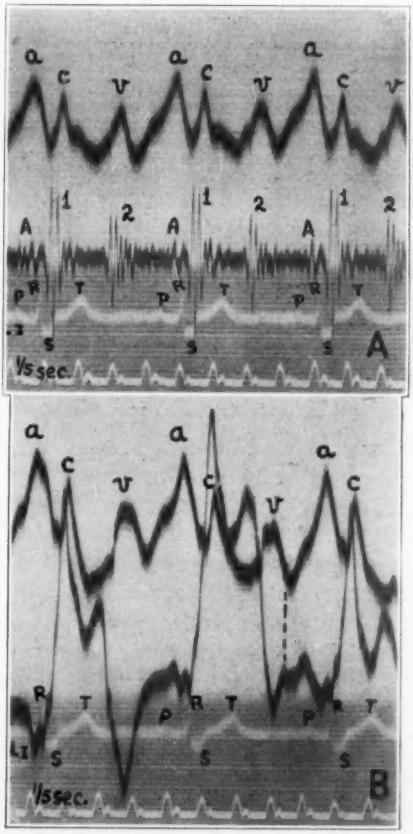

Fig. 16.—Optical records (*A*) of the venous pulse together with the heart sounds and (*B*) of the venous pulse together with the apex beat in a case in which the electrocardiogram was characterized by an abnormally long QRS interval and by broad S deflections in lead I. No signs of ventricular asynchronism were seen (time, 0.2 second).

there were obvious signs that the right ventricle contracted first, thereby really indicating left bundle branch block. In the other 2 cases no signs of asynchronism could be detected (fig. 15).

Of the 3 cases in which the electrocardiographic records were characteristic, according to Wilson and his associates,[16] of right bundle branch, in 1 a clear precedence of the left ventricle was actually found, but in the remaining 2 cases all signs of asynchronism were lacking (fig. 16).

From these observations the following conclusions may be drawn:

1. When left bundle branch block is present the electrocardiogram shows a tall, broad S in lead III.

2. Right bundle branch block may exist when the alterations described by Wilson and his associates [16] as characteristic of right bundle branch block are present.

3. Electrocardiograms with the characteristic features of bundle branch block may not be accompanied by signs of ventricular asynchronism.

This last assertion has considerable value, for we [4] have experimentally proved that whenever the section interrupts completely one of the bundle branches, marked ventricular asynchronism follows. On the other hand, whenever after section of a branch an electrocardiographic alteration appeared but no asynchronism could be detected, postmortem examination proved that the bundle branch had not been completely interrupted.

SUMMARY AND CONCLUSIONS

Bundle branch block experimentally produced in dogs is followed by marked ventricular asynchronism, and it may be assumed that the same happens in human beings with bundle branch block.

Optical recording of the apex beat, the venous pulse, the heart sounds and the central arterial pulse simultaneously makes it possible to recognize whether or not the ventricles beat synchronously or, in the absence of synchronism, which ventricle contracts first.

Investigations carried out in this way have demonstrated that the electrocardiographic alterations which, according to the older view, were considered as characteristic of right bundle branch block are in fact encountered in cases of left bundle branch block.

Electrocardiograms with all the characteristics of bundle branch block may exist without there being any detectable asynchronism and hence without there being complete block.

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16. Wilson, F. N., and others: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S Deflections in Lead I, Am. Heart J. **9**: 459, 1934.

In conclusion, it may be advanced that the electrocardiogram which shows pronounced alterations affords good evidence of intraventricular block. However, it does not offer a reliable means for establishing a diagnosis of complete bundle branch block or, furthermore, for the localization of the branch involved. The adequate recording of the mechanical events due to cardiac action affords the only means for determining the existence of ventricular asynchronism, thereby allowing the recognition of delayed excitation through one of the bundle branches and the localization of the functional disturbance.

NEUTROPHILIC LEUKOCYTOSIS IN SPINAL FLUID ASSOCIATED WITH CEREBRAL VASCULAR ACCIDENTS

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The present paper records 6 cases in which softening or hemorrhage within the brain was associated with the presence of polymorphonuclear neutrophilic leukocytes in the spinal fluid in such numbers as to suggest the diagnosis of meningitis or at least of some degree of meningeal irritation. We believe that this leukocytosis represents an aseptic reaction of the meninges to the damage within the brain. Except for the first, the cases are reported in slight detail for sake of brevity.

REPORT OF CASES

CASE 1.—L. L., a Negress aged 49, was admitted to the medical service of the Baltimore City Hospitals on Sept. 13, 1937, in a moribund state. The only history available was that the patient went to bed on Saturday night, September 11, in her usual state of health, which was excellent. Apparently she lost consciousness during the night and never regained it. There was no history of hypertension or any previous illness.

Physical Examination.—The temperature was 100 F. (rectal), the pulse rate 92 and the respiratory rate 28. The patient was a middle-aged Negress, well developed and nourished. She was in a state of coma, from which she could not be aroused. The respirations were of the Cheyne-Stokes type. There were moderate retraction of the head and marked rigidity of the neck. The eyes looked to the right and did not move beyond the midline. The right pupil was smaller than the left, and both reacted sluggishly to light. The fundi appeared normal except for some fulness of the veins. The lungs were clear on percussion and auscultation. The heart was not enlarged, and no murmurs were noted. The

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blood pressure was 155 systolic and 110 diastolic. The right arm and leg were moved spontaneously, and there was no spasticity. The left arm and leg were slightly spastic and were never noted to move at all. The reflexes were hyperactive on both sides, and there was bilateral plantar extension. Kernig's sign was present.

Laboratory Data.—The urine had a specific gravity of 1.013 and gave a 3 plus reaction for albumin; microscopically only 7 to 8 white cells and a rare hyaline cast were noted. The blood count was as follows: red cells 4,260,000; hemoglobin 13.7 Gm.; white cells 19,200, predominantly polymorphonuclear. The nonprotein nitrogen was 46 mg. per hundred cubic centimeters. Lumbar puncture revealed a pressure of 175 mm. of water, with a definitely positive Pandy reaction and a cell count of 2,000, of which 95 per cent were polymorphonuclears. No organisms were seen on smear, and none were grown on culture. Blood cultures were negative. The result of the Eagle precipitation test was negative, and the Wassermann reaction of the spinal fluid was anticomplementary. The colloidal mastic test gave the reaction of 5555555554.

Clinical Course.—The case was considered as possibly one of meningitis or of ruptured abscess of the brain with leptomeningitis. Immediately after the lumbar puncture 30 cc. of antimeningococcus serum was given intrathecally. Lumbar punctures were instituted twice a day and serum given. The cell counts on successive punctures were 3,700; 7,200; 16,000; 10,800, and 9,400, with 88 to 95 per cent polymorphonuclear cells. Some of the increase was naturally attributed to the administration of the serum. No red blood cells were found. Repeated smears and cultures of the spinal fluid revealed no organisms. On the second day after admission 300 cc. of 0.8 per cent sulfanilamide was given subcutaneously, and this dose was repeated daily. The patient never regained consciousness. Her temperature gradually rose to 106 F., and she died on the fifth day after hospitalization.

Gross Examination at Autopsy.—Scattered small patches of consolidation were seen in the lungs. Both ovaries were practically replaced by what were obviously dermoid cysts.

Brain: The convolutions of the brain were flat. The meningeal veins were filled with blood, but there were no hemorrhages in the leptomeninges. On coronal section at the level of the mamillary bodies a large excavation filled with dark, friable blood clot was observed. It occupied the region of the globus pallidus, putamen and external capsule on the right side and measured 2.5 cm. across. It extended only 1 cm. posterior to the mamillary body, where it ended as a small, soft, necrotic area in the white matter of the temporal lobe. Proceeding anteriorly from the mamillary body, the hemorrhage expanded into the white matter of the parietal region. The internal capsule, caudate nucleus and lateral ventricle were markedly pushed to the left. There was no evidence of escape of blood into the ventricle other than slight staining of its lining. The widest portion of the clot was situated at a point approximately 1 cm. posterior to the tip of the temporal lobe. Here it measured 4 by 3.5 cm. and extended to a point 12 mm. from the temporal cortex. It almost completely replaced the island of Reil at this point, so that only a small rim of cortex remained. The hemorrhage became narrower as it passed into the frontal white matter, and 3.5 cm. from the anterior pole of the frontal lobe it connected with another clot in the white matter. This smaller area likewise contained dark clotted blood and measured 2.5 by 1.5 cm. at the level of the genu of the corpus callosum. The entire length of the larger

hemorrhage was 7 cm. The left hemisphere showed no gross pathologic changes. The larger cerebral arteries showed only a small amount of intimal sclerosis, while the smaller vessels were markedly affected.

Microscopic Examination at Autopsy.—There was lobular pneumonia, scattered groups of alveoli containing moderate numbers of polymorphonuclear leukocytes and serum. Sections of the right ovary showed in the wall of the cyst a small mass of recognizable ovarian tissue. Nearby the wall enclosed a small mass of cartilage, atrophic hair follicles and hair. In most places the lining of the cyst had disappeared. In other areas there was a low, flattened squamous epithelium.

Brain: The hemorrhage and the destruction of the adjacent tissues of the brain noticed grossly were accentuated microscopically. The blood had burrowed through the white matter but had not ruptured into the ventricle or surrounding perivascular spaces. In the region of the large hemorrhage there were rather numerous smaller, satellite hemorrhages and areas of fresh necrosis. The lateral portion of the internal capsule was necrotic. The putamen and globus pallidus were almost completely replaced by the clotted blood. The cerebral white matter in contact with the hemorrhage was necrotic and contained an infiltration of polymorphonuclear leukocytes, mononuclear cells and a small number of wandering phagocytic cells containing blood pigment. This picture was seen throughout the margin of the hemorrhage. In the anterior portion of the pons was another small area of fresh encephalomalacia, with a few polymorphonuclear leukocytes in it. The lateral ventricle, on the right side, contained a small number of leukocytes but no blood.

The small arteries showed all the degrees of sclerosis from slight thickening and fatty infiltration of the intima to complete calcification of the wall. Some of the vessels were nearly occluded by annular, sclerotic plaques. No thrombi were seen. The changes were more prominent in the vessels surrounding the hemorrhage. In the perivascular spaces also were small numbers of polymorphonuclear leukocytes. These too were more abundant in the region of the hemorrhage.

The meninges were only slightly thickened but contained diffusely scattered or occasionally clumped polymorphonuclear leukocytes. These were most numerous in the meninges over the right convexity, and the right side of the pons and cerebellum. They were seen to a lesser degree over the convexity of the unaffected left cerebral hemisphere. Fairly numerous large mononuclear cells also were present. There was no hemorrhage in the meninges. Bacterial stains did not reveal the presence of organisms. While the slight inflammatory changes in the substance of the brain about the hemorrhage were probably due to the destruction of the brain tissue, part or most of the meningeal infiltration cannot be interpreted as such, because of the injections of serum.

Anatomic Diagnosis.—Arteriosclerosis was generalized but was especially marked in the small cerebral vessels. A massive cerebral hemorrhage occupied the right parietal and frontal lobes. There was evidence of aseptic meningitis, cerebral and spinal, which had followed intraspinal injection of serum. Slight lobular pneumonia, chronic cystitis and pyelitis, bilateral dermoid cysts of the ovaries and sickle cells were observed in the spleen.

Case 2.—A 61 year old Negress, complaining of headache of two weeks' duration, with a history of right hemiparesis and of hypertension, had a blood pressure of 228 systolic and 126 diastolic, residual right hemiparesis, a positive Wassermann reaction and polymorphonuclear leukocytosis in the spinal fluid,

with a count of 1,600 cells, of which 85 per cent were polymorphonuclear neutrophils and 15 per cent lymphocytes. While in the hospital she became delirious, and cervical rigidity developed. Her temperature rose to 104 F. She became stuporous and died on the tenth day in the hospital. Autopsy revealed multiple old and recent areas of encephalomalacia due to cerebral thrombosis.

CASE 3.—A 64 year old white woman, with a history of hypertension, experienced tingling in the right arm and leg and subsequently lost consciousness. She presented elevation of temperature, a blood pressure of 260 systolic and 120 diastolic, moderate cervical rigidity, a turning of the head and eyes to the left, complete right hemiplegia and a cloudy spinal fluid containing 2,200 leukocytes, 86 per cent of which were polymorphonuclears. The fluid later became clear and showed only 8 lymphocytes. The patient regained consciousness on the fifth day in the hospital, but showed motor aphasia. She died of terminal bronchopneumonia. No autopsy was performed.

CASE 4.—A 49 year old Negro, with a history of abdominal pain and delirium, presented an enlarged heart and auricular fibrillation, with normal reactions on neurologic examination. On the second day he became stuporous, and cervical rigidity developed. The spinal fluid was cloudy and contained 890 leukocytes, of which 95 per cent were polymorphonuclears. The cells disappeared in three days. Later left hemiplegia developed, and the patient died on the twelfth day in the hospital. Autopsy disclosed arteriosclerotic disease of the heart, mural thrombi, multiple visceral infarcts and embolism or thrombosis of the right middle cerebral artery with a large hemorrhagic infarct in the right temporal lobe.

CASE 5.—A 64 year old white man with right hemiplegia and aphasia of four days' duration presented Cheyne-Stokes respirations, slight cervical rigidity, right hemiplegia, and a cloudy spinal fluid with moderate polymorphonuclear leukocytosis (472 leukocytes). The cells practically disappeared from the spinal fluid in five days. No clinical improvement was noted, and the patient died on the sixteenth day in the hospital. No autopsy was performed.

CASE 6.—A 60 year old Negro with a history of headaches and dizzy spells became unconscious a few hours before admission. He was stuporous, with cervical rigidity, a positive Kernig sign, hypertension and arteriosclerosis; left hemiplegia and hemianesthesia involved mainly the face and arm. Serologic tests gave negative results. The spinal fluid was cloudy, with 1,000 polymorphonuclear leukocytes; these disappeared gradually, and a slight mononuclear response followed. Consciousness and motor function gradually returned.

REVIEW OF THE LITERATURE

Since 1891, when Quinke performed the first lumbar puncture and cleared the way for study of the cerebrospinal fluid, various observations have been made on the occasional occurrence of polymorphonuclear leukocytosis in cases of acute cerebral softening due to various causes mechanical in nature. The literature contains relatively little information on leukocytosis in association with cerebral hemorrhage and thrombosis.

The earliest observations are to be found in the French literature. In 1902 Widal and Lemaire [1] reported 2 cases of dementia paralytica with lymphocytic reaction in the spinal fluid in which the sudden development of hemiplegia was followed by marked polymorphonuclear responses. In 1 case the leukocytosis disappeared with recovery from the cerebral accident, while in the other autopsy revealed a massive intracerebral hemorrhage bordering on the lateral ventricle. In 1911 Claude and Verdun [2] reported the case of a 62 year old man with sudden onset of coma and a meningeal syndrome but no localizing signs. The spinal fluid was turbid and contained a predominance of polymorphonuclear cells. He was treated for meningitis but subsequently died, at which time autopsy revealed an old hemorrhage in the occipital lobe and a more recent hemorrhage in the parietotemporal region with no evidence of septic meningitis. Rendu and Flandin [1] in 1912 reported a case of cerebral hemorrhage in which two successive episodes were associated with meningeal phenomena, both clinical and cytologic. In the same year Babinski and Gendron [3] reported 3 cases of polymorophonuclear leukocytosis. Two of these were cases of cerebral embolism secondary to rheumatic heart disease. Eschbach,[1] Claude,[1] Oury [1] and Globus and Strauss [4] subsequently added other cases of thrombosis and hemorrhage in which the same characteristics were presented and several patients showed signs of meningeal irritation.

The first thorough review of the subject was made by Claude and Oury [5] in 1923. They classified the different types of meningeal reaction, discussing those particularly associated with focal lesions of the brain, and reviewed all the cases previously reported. They stated that in these aseptic meningeal reactions the cell counts may vary from 40 to 10,000 polymorphonuclear cells per cubic millimeter and that serial punctures show a decrease in the number of cells corresponding to the clinical improvement.

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1. Cited by Claude and Oury.[5]

2. Claude, H., and Verdun, M.: Syndrome méningé subaigu avec réaction leucocytaire aseptique du liquide céphalo-rachidien au cours des hémorrhagies cérébrales frustes sous-épendymo-corticales, Bull. et mém. Soc. méd. d. hôp. de Paris **32**:68, 1911.

3. Babinski, J., and Gendron, A.: Leucocytose du liquide céphalo-rachidien au cours du ramollissement de l'écorce cérébrale, Bull. et mém. Soc. méd. d. hôp. de Paris **33**:370, 1912.

4. Globus, J. H., and Strauss, I.: Vascular Lesions and Tumors of the Brain: Difficulties in Differential Diagnosis, Arch. Neurol. & Psychiat. **15**:568 (May) 1926.

5. Claude, H., and Oury, P.: Réactions méningées et épanchements méningés puriformes aseptiques au cours des lésions en foyer de l'encéphale, Gaz. d. hôp. **96**:717, 1923.

In 1931 Cone and Barrera [6] reported the experimental production of cerebral infarcts in dogs by the injection of sterile emboli into the carotid arteries. Twenty dogs showed clinical signs of cerebral embolism, and in all these there was polymorphonuclear infiltration of the infarcts and surrounding areas, the earliest study being made eight and one-half hours after the insult. In 6 of the dogs neutrophils were seen in the spinal fluid at the time of death, the counts ranging from 371 at twenty-four hours to 1,135 at seventy-two hours after the occurrence of embolism. They concluded that polymorphonuclear cells pour into the infarcted area of the brain and overlying meninges within eight and a half hours after the occlusion of a vessel and reach their maximum at forty-eight hours. These cells reach the spinal fluid by way of the perivascular spaces, by direct invasion of the subarachnoid space or by extension into the ventricles.

Merritt and Fremont-Smith,[7] discussing alterations in the spinal fluid, stated that, in addition to inflammatory processes, various lesions associated with degeneration of the central nervous system, especially in proximity to the ventricular or subarachnoid surfaces, may be associated with slight or even moderate leukocytosis. High counts, however, are rare, but they cited 6 of 14 cases in which clear fluids showed white cell counts ranging from 50 to 1,900 polymorphonuclear cells.

COMMENT

When a stuporous or delirious patient with signs of meningeal irritation is found to have a great increase in cells in the spinal fluid, especially if the cells are predominantly polymorphonuclear, one naturally thinks first of some form of acute meningitis, and the tendency is to treat the condition as such, even when organisms cannot be demonstrated either by smear or by culture. It is not generally recognized however, that acute cerebral softenings resulting from noninfectious causes sometimes give the same clinical picture. The present paper reports 6 cases of vascular lesions of the brain in which signs of meningeal irritation were present and the spinal fluid showed large numbers of polymorphonuclear cells but no red blood cells or only negligible numbers of the latter. In none of these cases was there definite clinical or postmortem evidence of an infectious process.

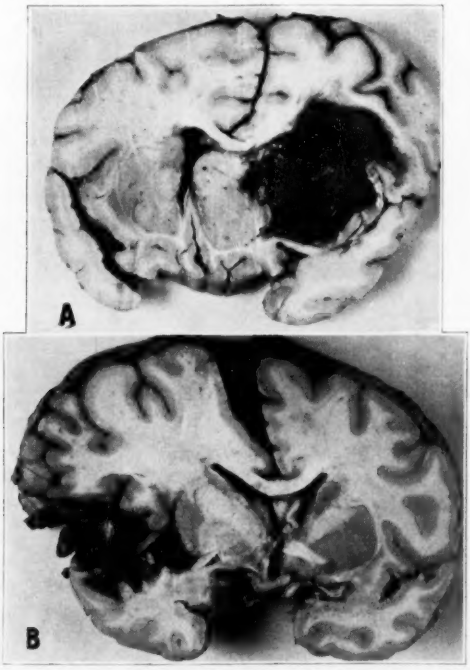
The first case is similar to that described by Claude and Verdun;[2] namely, there were a sudden onset of coma and a meningeal syndrome

6. Cone, W., and Barrera, S. E.: The Brain and Cerebrospinal Fluid in Acute Aseptic Cerebral Embolism: Experimental and Pathologic Study, Arch. Neurol. & Psychiat. **25**:523 (March) 1931.

7. Merritt, H. H., and Fremont-Smith, F.: The Cerebral Spinal Fluid, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1926, 1934, p. 555L.

but no localizing signs. The spinal fluid was turbid and contained a predominance of polymorphonuclear cells. The patient was treated for meningitis and died, and autopsy revealed a massive cerebral hemorrhage in the right parietal and frontal lobes (see figure, *A*).

The second case was one of infarction, multiple in nature, but localizing signs suggested a vascular accident. Later a meningeal syndrome developed, and meningitis was considered. On this occasion, however, our previous experience aided materially in making a correct diagnosis, which was borne out by postmortem examination.



Coronal sections of the brain (*A*, case 1; *B*, case 4), showing a large excavation in the right cerebral hemisphere filled with a blood clot. In case 1 there was no evidence of escape of blood into the ventricle. In case 4 the brain tore readily on its removal, as the cortex overlying the area of hemorrhage was thin. (The photographs were taken by permission of Mr. Milton Kougl.)

The fourth case is somewhat similar to the first, except that signs of hemiplegia eventually developed and a diagnosis of vascular accident was made. Autopsy showed an infarct in the right temporal lobe due to thrombosis of the right middle cerebral artery. It is to be noted that the cells disappeared from the spinal fluid before death.

In cases 3, 5 and 6 localizing signs occurred, plus similar leukocytosis in the spinal fluid, and in view of our previous experience we feel justified in considering them similar to the 3 cases in which postmortem examinations were made.

Some idea of the frequency of this phenomenon may be deduced from the fact that during the period covered by our observations, approximately nine months, 43 patients were admitted to the Baltimore City Hospitals who had had cerebral accidents recently (i. e., not over a week before) and in whom signs of meningeal irritation or changes in the spinal fluid were lacking. Our 6 cases thus represent an incidence of approximately 12 per cent of the group in which the findings might be expected.

From these cases and similar ones described by others, it seems that in cases of vascular lesions of the brain, whether hemorrhage or thrombosis, the clinical manifestations may be variable, ranging from an acute meningeal syndrome to localizing signs and a history compatible with cerebral vascular accident, with leukocytosis revealed only by lumbar puncture. The spinal fluid in these cases may show an abundant cellular response with polymorphonuclear leukocytes, giving a cloudy fluid suggestive of meningitis, or only a microscopic reaction, with polymorphonuclears or a low mononuclear count. Serial punctures in the course of the illness will show a gradual decrease in the number of cells, and the spinal fluid may eventually become normal. In cases in which only mononuclear cells appear, the "purulent" stage has been missed, and the fluid is returning to normal, or the meningeal reaction has been slight from the beginning.

In view of the experimental work of Cone and Barrera,[6] it seems fair to explain these meningeal reactions on the basis of leukocytic response around the foci of softening or hemorrhage. These cells probably reach the perivascular spaces, the subarachnoid space or the ventricles, according to the location of the lesion. When the lesion is small and deeply situated the cells probably never get to the periphery, and consequently the spinal fluid remains clear.

In the cases in which postmortem examination was performed, the necrotic regions showed a varying degree of infiltration with polymorphonuclear leukocytes, mononuclear cells and a small number of wandering phagocytes containing blood pigment. Our first patient, who died early in the course of her illness, showed the greatest degree of infiltration with polymorphonuclear leukocytes. The meningeal reaction in her case was probably augmented by administration of antimeningococcus serum.

It is to be expected that observations in these cases should fall in line with the experimental data already mentioned and that after the

vascular accident polymorphonuclear cells should pour into the affected area. Hence, postmortem examination during the early phase would show a predominantly polymorphonuclear infiltration, while during the later phases the infiltration would consist of mononuclear and phagocytic cells.

SUMMARY

Six cases of cerebral softening and cerebral hemorrhage in which a great excess of polymorphonuclear leukocytes was found in the spinal fluid are described.

We believe that this leukocytosis is due to an aseptic meningeal reaction to adjacent areas of necrosis within the brain.

It is only in cases in which the lesion is close to the surface of the cortex or approaches the wall of the ventricle that leukocytosis occurs, for deeply seated lesions cause no such reactions in the spinal fluid.

The leukocytosis usually begins within several hours after the infarction and gradually disappears within the next five to six days. The number of cells varies between 50 and 3,000 or more per cubic millimeter.

In cases in which the leukocytosis is great there may be stiffness of the neck and a positive Kernig sign, i. e., clinical evidence of meningeal irritation.

In cases in which the vascular lesion does not cause demonstrable focal signs leukocytosis of this type in the spinal fluid may result in an erroneous diagnosis of meningitis.

Other writers have made similar observations, and a brief discussion of the literature is appended.

The cases are published by permission of Dr. T. R. Boggs.

NOTE.—Since completion of our study a case similar to those we have described was brought to our attention. By permission of Drs. W. T. Longcope and W. G. MacCallum, we give a brief summary of this case from the medical service of the Johns Hopkins Hospital.

H. R., a 35 year old woman, had a sudden onset of blindness, followed by gradually developing stupor. She showed signs of left hemiplegia. The spinal fluid on her admission was normal, but four days later cervical rigidity and a positive Kernig sign developed. The lumbar puncture was not repeated, but at autopsy a thick, purulent exudate in the meninges overlay the occipital lobes and the anterior surface of the cerebellum on both sides. Areas of encephalomalacia were noted beneath these exudates in the occipital lobes, in the cerebellum and also in the right internal capsule. There was extreme cerebral arteriosclerosis, but no large thrombosed vessel was observed to account for the infarcts. Microscopically the exudate, which consisted entirely of polymorphonuclear leukocytes, was seen to extend into numerous sulci and to involve the superficial portion of

the cortex and the perivascular spaces of the small vessels to the underlying parenchyma. Cultures of the blood and the cerebrospinal fluid, as well as bacterial stains of the exudate, failed to reveal any organisms.

We believe that this case falls into the group which we have discussed and that if a lumbar puncture had been done at the time when meningeal signs developed, it would have shown the presence of polymorphonuclears in the fluid. The case is of particular interest in that the course of the cells was traced directly from the softened areas of the brain, via the perivascular spaces and overlying cortex, to the subarachnoid space.

STUDIES OF UROBILINOGEN

I. A SIMPLE AND RAPID METHOD FOR QUANTITATIVE DETERMINATION OF UROBILINOGEN IN STOOL AND IN URINE

ROBERT SPARKMAN, M.D.
CINCINNATI

Estimations of the urobilinogen content of stool and of urine afford information regarding the state of hepatic function, the patency of the extrahepatic biliary passages and the rate of destruction of red cells.

The potential clinical value of estimations of urobilinogen has generally been inadequately realized. This has been due in large part to the lack of a method sufficiently simple and rapid to be within the scope of the average clinical laboratory and yet sufficiently accurate to afford dependable results.

No attempt will be made to review the numerous procedures which have been devised for the quantitation of urobilinogen. This information may be obtained from the reviews and methods of Wilbur and Addis,[1] Terwen,[2] Wallace and Diamond,[3] Elman and McMaster,[4] Watson,[5] Scott,[6] Naumann[7] and Farmer.[8]

This work was aided by a grant from the Fraser Fund.

From the Laboratories of Baylor University Hospital, Department of Pathology, Baylor University College of Medicine, Dallas, Texas.

1. Wilbur, R. L., and Addis, T.: Urobilin: Its Clinical Significance, Arch. Int. Med. **13**:235 (Feb.) 1914.

2. Terwen, A. J. L.: Ueber ein neue Verfahren zur quantitative Urobilin Bestimmung im Harn und Stuhl, Deutsches Arch. f. klin. Med. **149**:72 (Nov.) 1925.

3. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test of Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

4. Elman, R., and McMaster, P. D.: The Quantitative Determination of Urobilin, J. Exper. Med. **41**:503 (April) 1925.

5. Watson, C. J.: (*a*) The Average Daily Elimination of Urobilinogen in Health and Disease, with Special Reference to Pernicious Anemia, Arch. Int. Med. **47**:698 (May) 1931; (*b*) Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458 (Sept.) 1936; (*c*) II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med. **59**:196 (Feb.) 1937; (*d*) III. Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, ibid. **59**:206 (Feb.) 1937.

6. Scott, L. D.: A Colorimetric Method for the Estimation of Urobilinogen in Urine and Feces, J. Lab. & Clin. Med. **18**:399 (Jan.) 1933.

(Footnotes continued on next page)

For accuracy of results, the method devised by Watson [5b] is unquestionably superior to any previously described. It has been modified by Naumann.[7b] Although much information regarding the physiologic and pathologic variations of urobilinogen of the stool and urine has been disclosed by the investigations of Watson,[5] the method employed is unsuited to general clinical use because of technical difficulty.

The method which has received the widest clinical acceptance is that of Wallace and Diamond.[8] This determination, however, is only roughly quantitative and is not well suited to estimation of urobilinogen in the stool.

A procedure is herewith presented for the quantitative determination of the urobilinogen of stool and urine. This method, because of its speed, simplicity and accuracy, is within the scope of any clinical laboratory and is therefore well adapted to clinical use.

METHOD

The method of estimating values of urobilinogen in stool and urine is dependent on the so-called aldehyde reaction, with the development of a red color on the addition of an acid solution of paradimethylaminobenzaldehyde (Ehrlich's aldehyde reagent) to solutions containing urobilinogen. This color is compared with an artificial standard prepared from gold chloride and sodium bromide.

The method of determining the urobilinogen of stool consists of aqueous emulsification of a weighed sample of stool, with reduction of urobilin to urobilinogen by ferrous sulfate and sodium hydroxide. The reduction is accelerated by incubation. This is followed by filtration, addition of Ehrlich's reagent and colorimetric comparison with the artificial standard after a suitable period has been allowed for the development of color.

Determination of the urobilinogen of urine is performed on fresh or suitably preserved specimens of urine; it consists of removal of bile pigment by addition of calcium chloride and filtration, with subsequent addition of Ehrlich's reagent to the filtrate. The residue on the filter is used in testing for bile pigment.

Aldehyde Reagent.—The aldehyde reagent consists of a solution of paradimethylaminobenzaldehyde in hydrochloric acid. The dilution of reagent employed, described by Wilbur and Addis,[1] is prepared as follows: Seventy-five cubic centimeters of concentrated hydrochloric acid and 75 cc. of distilled water are mixed and added to 10 Gm. of paradimethylaminobenzaldehyde. A sample of reagent prepared in this manner has shown no deterioration after eight months.

Artificial Standards.—An artificial standard is prepared by the addition of a solution of sodium bromide to a solution of gold chloride. Three strengths of this standard are employed. The three dilutions cover the range of most determinations of both fecal and urinary urobilinogen. The color is suitable for comparison with

7. Naumann, H. N.: (*a*) Studies on Bile Pigments: I. A Study of Ehrlich's Test for Urobilinogen and Schlesinger's Reaction for Urobilin, Biochem. J. **30**:347 (March) 1936; (*b*) III. The Quantitative Determination of Urobilin and Urobilinogen in Urine and Feces, ibid. **30**:1021 (June) 1936.

8. Farmer, L.: A Method for the Quantitative Determination of Urobilinogen in the Urine, J. Lab. & Clin. Med. **22**:1277 (Sept.) 1937.

aqueous and urinary solutions and with fecal extracts of urobilinogen. The following stock solutions are prepared: (1) a 4 per cent aqueous solution of gold chloride and (2) a 10 per cent aqueous solution of sodium bromide.

The three dilutions of standard are prepared from the stock solutions as follows:

1. Strong Standard: One volume of sodium bromide is added to 1 volume of gold chloride, and the resultant solution is made up to 15 volumes with distilled water.

2. Intermediate Standard: This standard is prepared by dilution of 1 volume of the strong standard with an equal volume of distilled water.

3. Weak Standard: The weak standard is prepared by dilution of 1 volume of the intermediate standard with an equal volume of distilled water.

Samples of these standards have shown no deterioration after eight months.

Evaluation of Standards in Terms of Crystalline Urobilinogen.—The values for the different strengths of standard in terms of milligrams of urobilinogen were determined by colorimetric comparison with known quantities of urobilinogen dissolved in weak solutions of sodium carbonate and treated with Ehrlich's reagent.

Crystalline urobilinogen was prepared from bilirubin (Eastman) according to the method of Fischer.[9] The product was identified by its physical and spectroscopic characteristics. The urobilinogen was weighed accurately and dissolved in a 0.5 per cent solution of sodium carbonate. Varying dilutions were prepared from the original solution of urobilinogen. To 10 cc. of each dilution 1 cc. of Ehrlich's reagent was added. Each of the three strengths of standard was compared in the colorimeter with the dilution of urobilinogen most closely resembling it in color, and the value of the standard in milligrams of urobilinogen per hundred cubic centimeters was computed therefrom. Crystalline urobilinogen was prepared a second time, and the standardization was repeated. The final values for the three standards were obtained by averaging the results determined on the two occasions. All procedures were carried out immediately after the preparation of crystalline urobilinogen and were performed in a subdued light. The results are recorded in table 1. Considering the instability of urobilinogen and the difficulty of its preparation, the figures for the two standardizations are in fairly close agreement.

TABLE 1.—*Evaluation of Standards in Terms of Crystalline Urobilinogen*

Standardization	Value of Standard, Mg. per 100 Cc.		
	Weak	Intermediate	Strong
First	0.966	2.730	8.960
Second	0.914	2.000	7.400
Average of first and second	0.935	2.365	8.175

As indicated by the figures in table 1, the values computed for the various standards are as follows: (*a*) strong standard, 8.175 mg. of urobilinogen per hundred cubic centimeters; (*b*) intermediate standard, 2.365 mg., and (*c*) weak standard, 0.935 mg.

For ease of calculation these figures were simplified to the nearest first decimal. The final values for the standards are therefore as follows: (*a*) strong standard, 8.2 mg. of urobilinogen per hundred cubic centimeters; (*b*) intermediate standard, 2.4 mg., and (*c*) weak standard, 0.9 mg.

9. Fischer, H.: Zur Kenntnis der Gallenfarbstoffe, Ztschr. f. physiol. Chem. **73**:204, 1911.

PROCEDURE FOR THE QUANTITATIVE DETERMINATION OF FECAL UROBILINOGEN

It is not essential that the determination be performed on fresh stool, since a stage is included whereby urobilin is reduced to urobilinogen. Stool should not be permitted, however, to undergo excessive desiccation. It is possible to perform determinations either on a single stool, expressing the result in terms of the concentration of urobilinogen in milligrams per hundred grams of stool, or on entire specimens collected over twenty-four or more hours, in which case the values for fecal urobilinogen may be expressed in terms of milligrams per twenty-four hour excretion. In this series of papers the former terminology is employed, for reasons which will be elaborated in the second article. The method for reduction of urobilin to urobilinogen is based on the procedure of Terwen [2] and its modifications by Watson [5] and Naumann.[7b] The detailed procedure for the quantitative determination of fecal urobilinogen follows.

Weigh 5 Gm. of the mixed stool on a wooden tongue depressor and, with the aid of a small sliver of wood, transfer it to a mortar. Emulsify the stool in 100 cc. of distilled water by gradual addition of the water and repeated transfer to a 250 cc. Erlenmeyer flask. Dissolve 8 Gm. of crystalline ferrous sulfate in 40 cc. of water and transfer, with mixing, to the emulsion of stool (this reagent should be freshly prepared). Add slowly 40 cc. of a 10 per cent solution of sodium hydroxide, rotating the flask during the addition. Stopper the flask and mix the contents by vigorous shaking. Place the flask and its contents in a water bath at a temperature of 50 C. Allow the flask to remain there fifteen minutes. Remove the mixture from the water bath and allow it to cool to room temperature, then filter (Whitman no. 2 filter paper is satisfactory). Pipet 5 cc. of the filtrate into a test tube. Add 5 cc. of distilled water, 0.3 cc. of five times normal hydrochloric acid and 1 cc. of Ehrlich's reagent. Allow five minutes for full development of the color. Compare the solution in a colorimeter with the standard of the nearest depth of color. The unknown solution should be read promptly after being placed in the colorimeter cup. Calculations are made as follows:[10] (*a*) If the strong standard is used, $R_s/R_u \times 630$ represents the number of milligrams of urobilinogen per hundred grams of stool; (*b*) if the intermediate standard is used, the formula is $R_s/R_u \times 185$, and (*c*) if the weak standard is used, the formula is $R_s/R_u \times 70$. The three standards cover all ranges of values for urobilinogen with the exception of extremely high ones. In the event that such concentrations are encountered, the procedure is repeated after suitable dilution of the filtrate.

Comment.—With the method proposed by Watson [5b] one hour is allowed for the reduction of urobilin to urobilinogen. This reduction

10. The numerical factors for the calculations listed are obtained in the following manner: The mixture of stool, water, ferrous sulfate and sodium hydroxide has an approximate volume of 187 cc. When the final addition of 5 cc. of water and 0.3 cc. of hydrochloric acid to 5 cc. of fecal filtrate is taken into account, the ultimate solution prior to the addition of Ehrlich's reagent represents 5 Gm. of stool in approximately 385 cc. of solution. The concentration of urobilinogen in milligrams per hundred grams of stool is therefore calculated by the formula, urobilinogen $= R_s/R_u \times F \times 3.85 \times 20$, in which F represents the urobilinogen equivalent of the particular strength of standard which is employed. The value for F is 8.2, 2.4 and 0.9 for the strong, the intermediate and the weak standard, respectively.

is allowed to proceed at room temperature. Naumann [7b] presented evidence to indicate that the reduction is dependent on the time factor, the reducing action reaching a peak in three hours at 20 C. or in five minutes at 35 C. In order to verify the acceleration of reduction at increased temperatures, 10 samples of stool were analyzed after they had been in the water bath for fifteen minutes at 50 C. and after they had stood for three hours at room temperature. The results of this study, which are presented in table 2, indicate that full reduction is obtained in the allotted period of incubation, supporting the statements made by Naumann.

The characteristic color reaction occurring on addition of Ehrlich's reagent to urobilinogen is due to the pyrrole group. The same color may be obtained by addition of Ehrlich's reagent to indole, which also

TABLE 2.—*Effect of Incubation on Reduction Time of Urobilinogen*

No. of Specimen of Stool	Concentration of Urobilinogen After 15 Minutes in Water Bath at 50 C., Mg. per 100 Gm.	Concentration of Urobilinogen After 3 Hours at Room Temperature, Mg. per 100 Gm.
1	215.6	212.4
2	212.4	206.5
3	222.6	222.6
4	81.0	81.4
5	254.5	276.0
6	206.5	224.2
7	228.4	238.6
8	162.3	166.7
9	187.0	184.0
10	96.0	91.0

posseses a pyrrole group. Indole is produced in the intestine by the action of putrefactive bacteria on protein; it is generally regarded as the fecal constituent most likely to induce error in determinations of fecal urobilinogen. Indole is very slightly soluble in water at room temperature, moderately soluble in hot water and readily soluble in ether or alcohol. In methods involving extraction of urobilinogen with ether or purified petroleum benzin it is necessary to include some process for avoiding the effect of indole. This is ordinarily accomplished by bringing about the aldehyde reaction in a medium of acetic acid rather than hydrochloric acid. Naumann,[7b] however, stated the belief that this expedient prevents only a part of the color produced by indole. With my method, owing to the relative insolubility of indole in aqueous solutions at room temperature, the degree of interference is slight and of little clinical significance. Convincing evidence of this fact has been obtained by analysis of 30 specimens of stool from 5 patients who were subsequently proved to have complete obstruction

of the common duct, which prevented any bile from reaching the intestine. In every instance color was absent after the addition of Ehrlich's reagent, a fact which effectively established the absence of both indole and urobilinogen. The small amount of bile which reaches the gastrointestinal tract from its bile-stained mucosa is insufficient to give a positive reaction in the test for urobilinogen with the method described.

In addition to the clinical evidence just cited, which indicated the negligible effect of indole, experimental evidence which led to the same conclusion was established. With the use of alcoholic solutions of indole it was found that on addition of Ehrlich's reagent the intensity of color produced per milligram of indole approximates that produced by an equal weight of urobilinogen. A saturated aqueous solution of indole, however, when treated with Ehrlich's reagent produces a color equivalent to that caused by only 0.9 mg of urobilinogen per hundred cubic centimeters. Indole was added to four portions of a sample of acholic stool in such quantities as to produce a concentration of 100, 200, 300 and 400 mg. of indole per hundred grams of stool, respectively. On subsequent analysis of these specimens of stool, the degree of color produced was equivalent to that caused by only 53.4, 56, 60.6 and 61.3 mg. of urobilinogen per hundred grams of stool, respectively.

It is thereby demonstrated that with my method indole is capable of producing some interfering effect but that the degree of interference is extremely slight and is apparently limited by the extent of the aqueous solubility of indole. Moreover, the results obtained from analysis of 30 samples of stool from 5 patients who had complete obstruction of the common bile duct indicate that the percentage of error induced by indole in clinical analysis is even considerably less than the small amount which can be produced experimentally.

PROCEDURE FOR QUANTITATIVE DETERMINATION OF URINARY UROBILINOGEN AND DETECTION OF BILE PIGMENT IN URINE

The method is applicable either to single specimens of urine or to specimens excreted during twenty-four hours or more. Single samples should be freshly voided. Twenty-four hour specimens are collected according to the method advocated by Watson,[5b] which consists of the employment of a brown glass bottle to which has been added about 100 cc. of purified petroleum benzin and 5 Gm. of anhydrous sodium carbonate. The details of the procedure follow.

To a small amount of urine in a flask add anhydrous calcium chloride in the proportion of 50 cc. of urine to 2 Gm. of the salt. Mix the combination well and filter. The residue on the filter is used in the detection of bile pigment, while the filtrate is used for the quantitative determination of urobilinogen.

Test for Bile Pigment.—Pour a few drops of concentrated nitric acid down the side of the filter. In the presence of bilirubin a colored zone is produced which consists of a central area of pink (choletelin) and a periphery of green (biliverdin). As much as five minutes may be necessary for full development of the color.

Determination of Urobilinogen.—Add 1 cc. of Ehrlich's reagent to 10 cc. of the filtrate and mix by several inversions. Allow five minutes for full development of the color. Match the sample promptly in a colorimeter with the standard which has the intensity of color nearest that of the unknown solution. With specimens containing unusually high concentrations of urobilinogen the procedure is repeated after suitable dilution of the filtrate. Calculations are made as follows: (*a*) When the strong standard is employed, $R_s/R_u \times 8.2$ represents the number of milligrams of urobilinogen per hundred cubic centimeters of urine; (*b*) when the intermediate standard is employed, the formula is $R_s/R_u \times 2.4$, and (*c*) when the weak standard is employed, the formula is $R_s/R_u \times 0.9$.

Comment.—The test for bile pigment is a modification of the Gmelin test. Concentration of bile pigment occurs through adsorption

TABLE 3.—*Relative Sensitivity of Standard Tests for Bile Pigment in Urine* *

Dilution of Urine	Results of Tests					
	Foam	Gmelin	Rosenbach	Huppert	Huppert-Cole	Adsorption with Calcium Chloride
None	Strongly positive	Strongly positive	Strongly positive	Strongly positive	Strongly positive	Strongly positive
1:10	Weakly positive	Weakly positive	Weakly positive	Positive	Weakly positive	Positive
1:20	Negative	Negative	Trace	Positive	Trace	Positive
1:40	.....	.....	Negative	Positive	Negative	Positive
1:80	.....	.....	.....	Weakly positive	.....	Weakly positive
1:160	.....	.....	.....	Trace	.....	Trace
1:320	.....	.....	.....	Negative	.....	Negative

* Hawk, P. B., and Bergeim, O., and others: Practical Physiological Chemistry, ed. 11, Philadelphia, P. Blakiston's Son & Co., 1937, p. 342.

to calcium chloride, which results in greatly increased sensitivity of the test. The sensitivity of this method was compared with that of standard methods by obtaining a specimen of urine which contained large amounts of bile and performing the various tests for bile pigments on progressively diluted portions of the original specimen. The results are recorded in table 3.

A simple and extremely sensitive test for bile pigment in the urine has been described by Naumann.[11] This is somewhat too sensitive for clinical purposes, however, since it demonstrates traces of bile even in normal urine. The sensitivity of the test just described seems well suited to clinical use. Significant quantities of bile can always be

11. Naumann, H. N.: Studies on Bile Pigments: II. A New Test for Bilirubin in the Urine and Its Use for Detection of Bilirubin in Normal Urine, Biochem. J. **30**:762 (May) 1936.

detected by this method, whereas other methods frequently fail to demonstrate the presence of bile.

It is generally agreed that in freshly voided urine it is unnecessary to employ a reducing agent, since inconsequential amounts of urobilin are present, practically all the chromogen having the form of urobilinogen. Moreover, I have obtained evidence which indicates that in urine preserved according to the method of Watson previously described oxidation of urobilinogen to urobilin over twenty-four hours is so slight as to be of no clinical significance. To establish this fact, 5 samples of urine were preserved under the conditions previously enumerated, and after twenty-four hours the urobilinogen content of each was determined with and without reduction by ferrous sulfate and sodium hydroxide. Only specimens having an abnormally high content of urobilinogen were employed. In no instance was there a significant loss

TABLE 4.—*Deterioration of Urobilinogen in Preserved Twenty-Four Hour Specimens of Urine*

No. of Specimen	Urobilinogen Content, Mg. per 100 Cc.	
	Without Reduction	After Reduction
1	11.71	11.78
2	7.13	7.25
3	10.45	8.82
4	20.50	19.22
5	9.11	10.24

of urobilinogen, as shown in table 4. For this reason no procedure is included for reduction of urobilin to urobilinogen in freshly voided or properly preserved urine.

Rarely, large quantities of protein in urine cause turbidity after the addition of Ehrlich's reagent. In such an instance the protein can be removed by mixing equal quantities of urine and a 3 per cent solution of sulfosalicylic acid and filtering.

GENERAL COMMENT

Filtrates obtained with the extraction of urobilinogen from feces are practically devoid of any pigment other than that due to urobilinogen, in consequence of which the methed described is equally accurate for high or low concentrations of urobilinogen.

In performing estimations of urinary urobilinogen as a source of information of clinical value, one is primarily concerned only with increases in concentration. With the exception of the removal of bile pigment to avoid turbidity, no attempt is made to free the urine of its coloring matter. Thus the values for urinary urobilinogen in the normal

range will be higher than those obtained by other methods. As the concentration of urinary urobilinogen increases, diminution of the error induced by other urinary pigments occurs, the error being inconsequenial when the pathologic range of urobilinogenuria is reached.

Methods employing extraction of urobilinogen by purified petroleum benzine or ether involve some loss of urobilinogen by incomplete extraction and by oxidation of the unstable chromogen on exposure to light. These sources of error are largely avoided with my method. Watson [5b] stated that in consequence of the instability of urobilinogen it is certain that no quantitative method can aspire to more than approximate values. This being true, any sources of error in the method described are more than offset by its speed and simplicity.

SUMMARY

A procedure is described for the quantitative determination of urobilinogen in stool and urine. The principal advantages of the method are simplicity, rapidity and clinical adaptability.

A sensitive test for bile pigment in the urine, consisting of a modification of the Gmelin test, is also described.

Dr. Benjamin Wells, of the department of physiologic chemistry, prepared crystalline urobilinogen on two occasions, and Dr. E. R. Hayes gave suggestions regarding the preparation of the artificial standards.

STUDIES OF UROBILINOGEN

II. NORMAL VALUES FOR EXCRETION OF UROBILINOGEN IN SINGLE SPECIMENS OF URINE AND STOOL

ROBERT SPARKMAN, M.D.
CINCINNATI

In the first article of this series a simple method was described for the quantitative determination of urobilinogen in stool and urine. This method is applicable to the analysis either of single specimens of urine and stool or of specimens collected over twenty-four or more hours.

The remarkable investigations of Watson[1] constitute the most outstanding contribution to the knowledge of the daily excretion of urobilinogen in health and disease. It is his belief that examination of single specimens of urine and stool is of little aid in diagnosis and that the potential clinical value of studies on urobilinogen can be realized only by determination of the total daily excretion of urobilinogen in stool and urine. The procedure which he employs involves the collection of one or more twenty-four hour specimens of urine and of entire specimens of stool for at least four days.

The clinical value of any type of procedure which requires the prolonged collection of entire specimens of stool is subject to obvious limitations. The same is true in a limited sense of the repeated collection of twenty-four hour specimens of urine. The diagnostic value of estimations of urobilinogen on single specimens of urine, particularly in the detection of impaired hepatic function and in the differential diagnosis of jaundice, has been established by the investigations of Wallace and Diamond,[2] Piersol and Rothman,[3]

This work was aided by a grant from the Fraser Fund.

From the Laboratories of Baylor University Hospital, Department of Pathology, Baylor University College of Medicine, Dallas, Texas.

1. Watson, C. J.: (*a*) The Average Daily Elimination of Urobilinogen in Health and Disease, with Special Reference to Pernicious Anemia, Arch. Int. Med. **47**:698 (May) 1931; (*b*) Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458 (Sept.) 1936; (*c*) II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med. **59**: 196 (Feb.) 1937; (*d*) III. Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, ibid. **59**:206 (Feb.) 1937.

2. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test of Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

3. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests, J. A. M. A. **91**:1768 (Dec. 8) 1928.

Rosenberg [4] and White.[5] Further evidence that significant clinical observations can be based on a knowledge of the concentration of urobilinogen in successive single specimens, particularly of stool, will do much toward placing this type of determination on a practical clinical basis.

The present article describes a series of quantitative determinations of the urobilinogen content of single specimens of urine and feces. The results of urinalysis are expressed in terms of the concentration of urobilinogen in milligrams per hundred cubic centimeters of urine. The concentration of fecal urobilinogen is expressed in terms of milligrams of urobilinogen per hundred grams of stool.

This study serves as a control for the method previously described and for the application of this method to clinical study, which will be dealt with in a subsequent article.

MATERIAL AND METHODS

The method employed for the determination of fecal and urinary urobilinogen is that described in the first article of this series. Color developed in fecal extract or in urine by the addition of Ehrlich's reagent is matched against an artificial standard prepared from gold chloride and sodium bromide. Three dilutions of the standard, designated as the strong, the intermediate and the weak, are available. The unknown solution is matched against the standard which it approximates most closely in intensity of color.

The control series of tests included 100 determinations of fecal urobilinogen and 200 determinations of urinary urobilinogen. Of the 100 samples of stool, 50 were obtained from ambulatory persons, apparently in good health, who represented all ages and both sexes. The remaining 50 were obtained from hospital patients who presented no evidence of hepatic disease, jaundice or significant alteration in the state of balance between production and destruction of red cells. The 200 specimens of urine consisted of two groups of 100 each, subdivided according to the same criteria.

RESULTS

In the first group of 50 samples of stool, obtained from ambulatory subjects, the average excretion of urobilinogen was 259.1 mg. per hundred grams of stool. Seventy-two per cent of the values for this series were between 150 and 300 mg. The highest and the lowest value encountered were 520 and 76.4 mg. per hundred grams, respectively.

4. Rosenberg, D. H.: Galactose and Urobilinogen Tests in Differential Diagnosis of Obstructive and Intrahepatic Jaundice, Ann. Int. Med. **8**:60 (July) 1934.

5. White, F. W.: Galactose and Urobilinogen Tests in the Differential Diagnosis of Painless Jaundice, Am. J. Digest. Dis. & Nutrition **4**:315 (July) 1937.

In the second group of specimens of stool, obtained from hospital patients, an average urobilinogen excretion of 201.9 mg. per hundred grams was observed. Sixty-six per cent of the values for this series were between 150 and 300 mg. The highest and the lowest value encountered were 600 and 72.6 mg. per hundred grams, respectively.

The composite of the two groups, representing 100 determinations, yielded a general average of 230.5 mg. of urobilinogen per hundred grams of stool, with values lying between 150 and 300 mg. in 69 per cent of the instances. Fifteen per cent of the results were below this range, while 16 per cent exceeded it.

The results are presented in table 1.

TABLE 1.—*Quantitative Determinations of Urobilinogen in 100 Specimens of Stool*

Urobilinogen, Mg. per 100 Gm. of Stool	Number of Subjects	
	Ambulatory	In Hospital
Below 100	2	5
100-150	2	6
150-200	11	20
200-250	16	11
250-300	9	2
300-350	1	2
350-400	3	0
400-450	0	2
450-500	2	1
500-550	3	1
550-600	1	1
Representative Values, Mg. per 100 Gm. of Stool		
Value	Ambulatory	In Hospital
Average*	259.1	201.9
Highest	520.0	600.0
Lowest	76.4	72.6

* General average for both groups, 230.5 mg. per hundred grams of stool.

Values obtained for urobilinogen in normal urine with the method employed are higher than with other methods, since no attempt is made to remove the pigments of the urine. The interfering effect of such pigments becomes inconsequential when the pathologic range of urobilinogenuria is reached.

For the first series of 100 samples of urine, obtained from ambulatory subjects apparently in good health, the average value was 2.22 mg. of urobilinogen per hundred cubic centimeters of urine. Ninety-six per cent of the specimens were in the color range of the weak or of the intermediate standard. For the remaining 4 per cent, which were in the color range of the strong standard, the highest value observed was 8 mg. Most of the specimens were voided in the afternoon.

The average for the second series of samples of urine, obtained from hospital patients, was 1.24 mg. of urobilinogen per hundred cubic

centimeters of urine. The lower average is accounted for by the fact that most of the specimens in this group were voided in the morning, at which time the excretion of urobilinogen is at its lowest point. Ninety-eight per cent of the samples were in the color range of the weak or of the intermediate standard. For the remaining 2 per cent, which were in the color range of the strong standard, the highest value observed was 7.36 mg.

Of the composite group of 200 specimens of urine, only 6, or 3 per cent, were in the color range of the strong standard. No bile pigment was detected in any specimen.

Detailed results for the series are presented in table 2.

TABLE 2.—*Quantitative Determinations of Urobilinogen in 200 Specimens of Urine* *

Urobilinogen, Mg. per 100 Cc.	Number of Subjects	
	Ambulatory	In Hospital
Below 1	22	54
1-2	17	33
2-3	47	10
3-4	10	1
4-5	0	0
5-6	0	0
6-7	1	1
7-8	3	1
Representative Values, Mg. per 100 Cc.		
Value	**Ambulatory**	**In Hospital Patients**
Average†	2.22	1.24
Highest	8.00	7.36

* The urine of 4 ambulatory subjects and 2 patients yielded a color which matched that of the strong standard.

† General average for both groups, 1.73 mg. per hundred cubic centimeters.

COMMENT

Normal values for fecal urobilinogen obtained by my method usually lie between 150 and 300 mg. of urobilinogen per hundred grams of stool. The extreme limits of normal values are 70 to 600 mg. With this method, results for single specimens of stool are usually approximately twice those obtained with Watson's method.[1c] The lower values obtained by Watson's method are unquestionably due in part to loss of some urobilinogen, either by incomplete extraction or by exposure to light. Watson concluded that the normal range for feces is between 40 and 280 mg. per day, usually being from 100 to 250 mg. The normal variation of the urobilinogen concentration of single specimens of stool as ascertained by my method is little wider than the variation in daily excretion of fecal urobilinogen.

Any specimen of urine yielding a color in the range of the weak or of the intermediate standard may be regarded as containing no increase of urobilinogen. In such a case it is recommended that the value be reported as "not increased" rather than numerically, since other urinary pigments induce some error for urobilinogen values in the normal range. Colors in the range of the strong standard should be regarded with suspicion, particularly if associated with a positive reaction to the test for bile pigment. Values exceeding 8 mg. per hundred cubic centimeters almost certainly represent pathologic urobilinogenuria.

SUMMARY

On the basis of results obtained by the examination of 100 specimens of stool and 200 specimens of urine, normal values have been established for the concentration of urobilinogen in urine and in stool according to the method described in the first article of this series.

STUDIES OF UROBILINOGEN

III. CLINICAL VALUE OF DETERMINATIONS OF UROBILINOGEN CONTENT OF SINGLE SPECIMENS OF URINE AND STOOL

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Three distinct types of clinical information can be derived from studies of fecal and urinary urobilinogen.

Estimations of the urobilinogen of the stool constitute the best single measure of the rate of destruction of red cells. Increase of urobilinogen in the urine is one of the first manifestations of hepatic disease. Combined estimations of the urobilinogen of the stool and of the urine furnish one of the few dependable means of distinguishing between jaundice of intrahepatic origin and jaundice arising from obstruction of the extrahepatic biliary passages.

In spite of their potential value, studies of fecal and urinary urobilinogen have not come into general clinical use. This is readily understood when one realizes that most methods for the determination of urobilinogen require several days for the collection of specimens and several hours for the analytic procedures themselves.

In the first article of this series there was described a simple and rapid method for the quantitative determination of the urobilinogen of stool and urine. In the second article it was shown how this method was employed to establish normal values for the urobilinogen concentration of single specimens of urine and stool.

In the investigation reported here an attempt was made to apply the procedure previously described to the study of the three types of condition just mentioned and to demonstrate that with each type significant information can be obtained from analysis of single specimens of urine and stool rather than of specimens saved for several days.

The importance of urobilinogen in supplying evidence of disturbed hepatic function was first established by von Müller.[1] The investi-

This work was aided by a grant from the Fraser Fund.

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1. von Müller, F.: Ueber Ikterus, Jahresb. d. schles. Gesellsch. f. vaterl. Kult. (Med. Sekt.) **70**:1, 1893.

gations of Elman and McMaster [2] furnished much of the physiologic and pathologic basis on which has been developed the clinical application of studies on urobilinogen.

Bilirubin is generally agreed to be derived from the hemoglobin of destroyed erythrocytes. This synthesis probably occurs in the reticuloendothelial system. On reaching the intestinal tract, bilirubin is converted to urobilinogen by the action of intestinal bacteria. The greater part of the pigment is excreted in the stool, either as urobilinogen or as its oxidation product urobilin. That portion of the urobilinogen not excreted in the stool is absorbed and is carried to the liver by the portal circulation. Most of the urobilinogen which reaches the liver is reexcreted or utilized, the remaining small amounts entering the systemic circulation and being excreted as urobilinogen in the urine.

In the absence of impediment to the passage of bile from the liver to the intestine, the quantity of fecal urobilinogen parallels the rate of erythrocytic destruction. Estimations of fecal urobilinogen are therefore of value in the study of the anemias, especially in distinguishing anemias of increased destruction from those of decreased production.

The ability to reexcrete or to utilize the urobilinogen absorbed from the bowel is impaired relatively early in the course of disease of the liver, so that hepatic damage is associated with increased excretion of urobilinogen in the urine. Thus estimations of urinary urobilinogen afford a sensitive test for the presence of damage to the liver.

Total obstruction of the extrahepatic biliary passages, with complete failure of bile to reach the intestine, is associated with absence of urobilinogen from feces and urine. Partial obstruction is usually accompanied by diminution in fecal and urinary urobilinogen. Determinations of urinary and fecal urobilinogen thereby provide a means of differentiation between jaundice of intrahepatic origin and jaundice arising from complete or partial occlusion of the extrahepatic biliary passages.

Many investigators have contributed to knowledge of the clinical significance of determinations of urobilinogen. Relatively few of these studies, however, have been based on the examination of single specimens. Such work has been confined almost exclusively to the examination of urine alone.

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2. Elman, R., and McMaster, P. D.: Studies on Urobilin Physiology and Pathology: I. Quantitative Determination of Urobilin, J. Exper. Med. **41**:503 (April) 1925; II. Derivation of Urobilin, ibid. **41**:513 (April) 1925; III. Absorption of Pigments of Biliary Derivation from the Intestine, ibid. **41**:719 (June) 1925; IV. Urobilin and the Damaged Liver, ibid. **42**:99 (July) 1925; V. Relation Between Urobilin and Conditions Involving Increased Red Cell Destruction, ibid. **42**:619 (Nov.) 1925; VI. Relation of Biliary Infections to the Genesis and Excretion of Urobilin, ibid. **43**:753 (June) 1926.

The most comprehensive study of this type was that of Wallace and Diamond,[3] in which the examination of single specimens of urine was performed in 1,220 cases. Conditions associated with pathologic urobilinogenuria were subdivided into two groups. In the first group, consisting of diseases involving the liver and the biliary tract, increases of urinary urobilinogen were observed in cases of catarrhal jaundice, cholangitis, acute yellow atrophy, hepatic cirrhosis, chronic passive congestion of the liver associated with chronic endocarditis, abscess of the liver when the suppurative process was generalized rather than confined to a solitary lesion, miliary tuberculosis involving the liver, metastases producing generalized carcinomatosis of the liver rather than localized nodular areas, and toxic states, such as eclampsia. Absence of urobilinogen from the urine was noted in cases of complete obstruction of the bile passages due to neoplasm, and the value of determinations of urobilinogen in differentiating between jaundice arising from this cause and jaundice arising from hepatic disease was noted. In the second group, consisting of hemolytic diseases, pathologic urobilinogenuria was observed in cases of hemolytic icterus, pernicious anemia, septic states, malaria, lead poisoning and other types of hemolysis produced by poisons.

Piersol and Rothman[4] used single estimations of urinary urobilinogen in the detection of hepatic damage and in the differential diagnosis of jaundice; they concluded that estimation of the urobilinogen of the urine is probably the most delicate single test for dysfunction of the liver. Rosenberg[5] employed single specimens of urine and concluded that the determination of the urobilinogen of the urine provides the most reliable means of differentiating between hepatic and extrahepatic types of jaundice. White[6] utilized estimations of the urobilinogen of single specimens of urine in the differential diagnosis of jaundice.

The studies of Elman and McMaster[2] were based on examination of twenty-four hour specimens of urine and stool. The same is true of the investigations of Wilbur and Addis.[7] These authors stressed the

3. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test of Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

4. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests, J. A. M. A. **91**:1768 (Dec. 8) 1928.

5. Rosenberg, D. H.: Galactose and Urobilinogen Tests in Differential Diagnosis of Obstructive and Intrahepatic Jaundice, Ann. Int. Med. **8**:60 (July) 1934.

6. White, F. W.: Galactose and Urobilinogen Tests in the Differential Diagnosis of Painless Jaundice, Am. J. Digest. Dis. & Nutrition **4**:315 (July) 1937.

7. Wilbur, R. L., and Addis, T.: Urobilin: Its Clinical Significance, Arch. Int. Med. **13**:235 (Feb.) 1914.

importance of fecal urobilinogen values as a guide to the amount of destruction of blood in the body. Increased excretion of urinary urobilinogen was noted in various types of damage to the liver, including hepatic cirrhosis, hepatic stasis, poisonings, acute yellow atrophy, pneumonia and infections. In cases of obstructive jaundice urinary urobilinogen was observed to be absent or insignificant. Its intermittent presence was interpreted as indicative of incomplete obstruction with concomitant damage to the liver. Increases of urobilinogen in urine and stool were noted in various hemolytic diseases.

The extensive investigations of Watson [8] furnished the most complete and exact information available regarding the excretion of fecal and urinary urobilinogen in health and disease. These studies were based on examination of ninety-six hour specimens of stool and repeated twenty-four hour specimens of urine. This author emphatically expressed his belief that estimations of urobilinogen are of little clinical value unless they express results in terms of twenty-four hour excretion. The studies of Watson confirmed and amplified previously known facts regarding the clinical significance of estimations of urobilinogen and disclosed in addition much new information of great value. Increases in fecal urobilinogen were noted in hemolytic diseases. In pernicious anemia a decrease of urobilinogen in stool and urine was observed to be coincident with reticulocytic response to liver therapy. Increased urobilinogen in the stool was observed in some instances of Hodgkin's disease and leukemia. Low values were encountered in cases of secondary hyperchromic anemia and in all the cases of hypochromic anemia investigated. The idea was expressed that increases of urinary urobilinogen associated with hemolytic jaundice were probably secondary to complicating hepatic damage. Jaundice due to stone was not accompanied by considerable increase in urinary urobilinogen unless complications were present, such as acute cholecystitis or cholangitis, biliary cirrhosis or severe anemia. With such a complication the actual amount of urobilinogen appearing in the urine was dependent to some extent on the degree of biliary obstruction and the consequent amount of urobilinogen formed in the bowel and released from it. Thus if obstruction was predominant urinary urobilinogen was diminished, whereas if the obstruction was slight and the hepatic damage

8. Watson, C. J.: (*a*) The Average Daily Elimination of Urobilinogen in Health and Disease, with Special Reference to Pernicious Anemia, Arch. Int. Med. **47**:698 (May) 1931; (*b*) Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458 (Sept.) 1936; (*c*) II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med. **59**:196 (Feb.) 1937; (*d*) III. Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, ibid. **59**:206 (Feb.) 1937.

considerable urinary urobilinogen was increased. Jaundice due to neoplastic obstruction of the extrahepatic biliary passages was characterized by complete obstruction, as evidenced by persistent absence of urobilinogen from stool and urine. This was in contradistinction to jaundice due to stone or diffuse hepatic disease. The latter was usually characterized by marked increase of urobilinogen in the urine. In some cases cirrhosis was accompanied by signs of increased destruction of blood, such as increase in fecal urobilinogen and regenerative anemia, often macrocytic.

Josephs [9] made extensive use of estimations of the urobilinogen of the stool as a measure of erythrocytic destruction. In his studies of the anemias the amount of urobilinogen in the urine was disregarded, since he considered it to be negligible. The author employed two day specimens of stool. He stated the belief that a proper interpretation of values for fecal urobilinogen presupposes a knowledge of the amount of hemoglobin in the body.

The 40 cases in my series were divided in three groups. The first consists of cases in which the estimations of urobilinogen were employed for the detection of hepatic dysfunction. In none of these cases was there more than slight jaundice. The second group consists of cases of severe jaundice in which estimations of urobilinogen were used as a means of differential diagnosis of jaundice. The third group consists of cases in which there was some abnormality in either production or destruction of erythrocytes; in this group estimations of urobilinogen were employed primarily as a measure of destruction of red cells.

With my method, preparations of stool or urine are matched colorimetrically against one of three strengths of an artificial standard, which collectively cover the color range of most specimens. These are designated as the strong, the intermediate and the weak standard.

According to this method, normal values for stool are usually between 150 and 300 mg. of urobilinogen per hundred grams of stool. The extreme limits of normal are 70 to 600 mg. of urobilinogen per hundred grams of stool. Urine in the color range of the weak or the intermediate standard is regarded as containing no increase of urobilinogen. Urine requiring comparison with the strong standard should be regarded with suspicion. The extreme upper limit of values for normal urine is 8 mg. of urobilinogen per hundred cubic centimeters.

A. DETERMINATIONS OF UROBILINOGEN IN THE DETECTION OF HEPATIC DYSFUNCTION

This group consists of 19 cases in which clinical jaundice was slight or not demonstrable.

The employment of determinations of urobilinogen in the detection of hepatic dysfunction is dependent on the diminished ability of the damaged liver to utilize or reexcrete the urobilinogen which is absorbed

9. Josephs, H. W.: Mechanism of Anemia in Infancy, Bull. Johns Hopkins Hosp. **51**:185 (Oct.) 1932; Urobilin Excretion of Infancy and Childhood: Relation to Blood Destruction and Formation, ibid. **55**:154 (Aug.) 1934.

from the bowel, as a result of which increased amounts of urobilinogen are excreted in the urine. Therefore estimations of urobilinogen for demonstration of impaired hepatic function are largely confined to examination of urine.

As in other tests for hepatic disease, impairment of this function is manifest much more strikingly with acute diffuse inflammatory lesions than with chronic, focal or degenerative lesions.

In most of the cases included in this group repeated estimations of urinary urobilinogen were performed. The single value given is in each instance the most representative. The results of this study are presented in table 1. In 2 cases of abscess of the liver there was marked elevation of urinary urobilinogen. In each the suppurative process

TABLE 1.—*Estimations of Urobilinogen in the Detection of Hepatic Dysfunction*

Case No.	Patient	Diagnosis	Urobilinogen, Mg. per 100 Cc. of Urine	Bile in Urine	Urobilinogen, Mg. per 100 Gm. of Stool	Icterus Index
1	O. C.	Abscess of liver	29.25	+	-	17.6
2	C. A. G.	Abscess of liver	32.8	+++	-	20.0
3	J. H.	Portal cirrhosis	9.3	+	80.0	13.3
4	W. D. E.	Portal cirrhosis	9.0	++	-	23.5
5	H. E. H.	Portal cirrhosis	20.4	++	53.2	23.7
6	M. S.	Portal cirrhosis	8.5	+	226.0	13.0
7	A. S.	Cholecystitis and hepatitis	26.6	++	83.7	-
8	L. T. M.	Cholecystitis and hepatitis	16.2	++	-	24.0
9	O. R. T.	Cholecystitis and hepatitis	16.4	+++	99.4	31.4
10	M. T. G.	Lobar pneumonia	11.8	++	-	10.7
11	E. C. B.	Lobar pneumonia	14.8	++	-	-
12	A. B.	Lobar pneumonia	31.0	++	-	-
13	S. S.	Bronchiectasis, severe	36.8	++	-	-
14	M. D.	Ether anesthesia, brain tumor	11.9	+	-	-
15	A. L. S.	Ether anesthesia, tonsillectomy	7.4	+	-	-
16	J. T. W.	Ethylene anesthesia, perianal abscess	14.8	++	-	-
17	J. T. B.	Bile duct carcinoma of liver	No increase	Absent	-	-
18	A. B. H.	Secondary carcinoma from ovary	7.88	+	-	17.6
19	P. S.	Secondary carcinoma from stomach	No increase	Absent	493.0	-

was generalized. In all 6 cases of portal cirrhosis urobilinogenuria was evident in the pathologic range. Two of these cases, in which the condition was accompanied by severe jaundice, are listed in the second group. In 3 cases of acute or subacute cholecystitis increases of urinary urobilinogen were demonstrated. In 10 cases of cholecystitis not included in the table no increase of urobilinogen was noted. Graham [10] recognized the presence of hepatitis in association with disease of the gallbladder and stressed the necessity of evaluating the state of hepatic function prior to operations on the biliary tract. Estimations of urinary urobilinogen probably furnish the most satisfactory means of obtaining this information. In 3 cases of lobar pneumonia and in 1 of severe bronchiectasis increased urinary urobilinogen was observed. In 3 cases

10. Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521 (May) 1918.

studies were made after administration of general anesthesia. In 2 of these significant increases of urinary urobilinogen were observed. In the third the urinary urobilinogen concentration of 7.4 mg. per hundred cubic centimeters, although just below the upper limit of normal values (8 mg. per hundred cubic centimeters), probably should be regarded as significant, since it was accompanied by the presence of bile pigment in the urine. In the 1 case of primary carcinoma of the liver which was observed there was no elevation of the urinary urobilinogen. Operation on the abdomen and biopsy revealed a small carcinoma of the bile ducts situated on the anterior surface of the right lobe of the liver. The small size of this tumor undoubtedly accounted for its failure to cause pathologic urobilinogenuria. In 2 cases of secondary carcinoma of the liver urobilinogen values were in the normal range, although in 1 of them the urobilinogen content of the urine was at the extreme upper limit of normal and the urine contained small amounts of bile pigment.

By daily estimations of urinary urobilinogen in the group of cases just described it was possible to obtain much information regarding the progress of the hepatic lesion.

It was observed with considerable interest that on every occasion in which urinary urobilinogen was increased above the normal range there was also a detectable amount of bile pigment in the urine. In most instances the quantities of bile pigment were not great enough to permit detection by ordinary means but were sufficient to give unquestionably positive results with the method of testing described in the first article of this series. In the cases in which determinations of the icterus index were available there was observed in each instance an elevation in the degree of icterus, usually into the subclinical range. Determinations of fecal urobilinogen, when performed, tended to give values in the lower extreme of the normal range.

B. ESTIMATIONS OF UROBILINOGEN IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

In consideration of any patient with obvious clinical jaundice of moderate or severe degree, one may assume that sufficient hepatic damage is present to cause pathologic urobilinogenuria. If, however, the bile passages are occluded, no increases of urinary urobilinogen will occur because of failure of bile to reach the duodenum. Therefore with obviously jaundiced patients the principal role of determinations of fecal and urinary urobilinogen is to aid in the differential diagnosis of jaundice rather than in the detection of hepatic dysfunction. Jaundice arising from disease of the liver is ordinarily associated with increases of urobilinogen in the urine. Jaundice arising from complete

obstruction of the extrahepatic biliary passages, as is usually the case with neoplastic obstructions, is accompanied by disappearance of urobilinogen from stool and urine. In jaundice caused by partial obstruction of the bile ducts, as with obstruction due to stone, fecal urobilinogen is decreased but rarely completely absent. In such cases urinary urobilinogen is usually decreased, but it may be increased if the obstruction is slight and is accompanied by considerable hepatic damage.

My series consists of 15 cases, including 5 cases of acute intrahepatic jaundice, 2 of chronic intrahepatic jaundice and 8 of jaundice due to obstruction of the extrahepatic biliary passages, in 5 of which the cause was neoplasm. The results of this study are presented in table 2.

In acute diffuse inflammations of the hepatic parenchyma, as typified by the so-called catarrhal jaundice, there is ordinarily a preliminary

TABLE 2.—*Estimations of Urobilinogen in the Differential Diagnosis of Jaundice*

Case No.	Patient	Diagnosis	Urobilinogen, Mg. per 100 Cc. of Urine	Bile in Urine	Urobilinogen, Mg. per 100 Gm. of Stool	Icterus Index
20	F. N.	Acute diffuse hepatitis.....	21.0	++++	205.0	211.0
21	L. C. M.	Acute diffuse hepatitis.....	13.3	+++	77.2	83.0
22	J. D. J.	Acute diffuse hepatitis.....	13.6	+++	92.3	104.0
23	J. L.	Arsphenamine hepatitis	14.3	++++	74.6	172.0
24	R. D. M.	Acute diffuse hepatitis.....	16.2	++++	75.2	91.0
25	B. E.	Portal cirrhosis	40.0	+++	86.9	67.0
26	F. H.	Portal cirrhosis	36.0	+++	185.0	73.0
27	T. E.	Carcinoma of head of pancreas..	No increase	++++	Absent	161.0
28	C. A. C.	Carcinoma of head of pancreas..	No increase	+++	Absent	119.0
29	B. K.	Carcinoma of head of pancreas..	No increase	+++	Absent	54.0
30	C. D.	Carcinoma of head of pancreas..	No increase	++++	Absent	67.0
31	C. I. L.	Carcinoma of head of pancreas..	No increase	++++	Absent	111.0
32	R. A. C.	Stone in common bile duct.....	No increase	+++	68.0	58.5
33	S. M. S.	Stricture of common bile duct...	No increase	++	40.0	70.0
34	S. E. N.	Stricture of common bile duct...	No increase	++++	53.0	133.0

rise of the level of urinary urobilinogen into the pathologic range. At the height of the disease complete intrahepatic obstruction commonly develops, so that urobilinogen disappears from the urine and stool. This obstructive stage is transient, usually being of three or four days' duration, during which time the icterus index attains its highest level. This phenomenon has been observed by Wallace and Diamond,[3] Piersol and Rothman,[4] Watson,[8] Rosenberg [5] and White.[6] According to their reports, none of these writers has known the obstructive period to exceed seven days. After the spontaneous relief of intrahepatic obstruction, urobilinogen reappears in the urine in greatly increased amounts, which diminish slowly as the hepatic inflammation and jaundice subside.

In my series 5 cases of acute intrahepatic jaundice were studied. In 1 of these jaundice was the result of arsphenamine hepatitis (case 23). In all cases of this group, with 1 exception (case 22), there was observed at the height of the jaundice a period of three to five days during which no urobilinogen could be detected in stool or urine. Urobilinogen

then reappeared first in the stool, and shortly thereafter large increases of urobilinogen were noted in the urine. After the spontaneous relief of intrahepatic obstruction jaundice subsided promptly in each instance, and urinary urobilinogen slowly returned to normal levels.

Five cases of neoplastic obstruction of the common bile duct were studied. It has been noted by Wilbur and Addis,[7] Wallace and Diamond,[8] Watson,[8d] Rosenberg [5] and White [6] that neoplastic obstruction of the common bile duct is practically always complete, whereas obstructions due to stone are rarely so. These authors found that the persistent absence of urobilinogen from the stool and urine which occurs in most instances of neoplastic obstruction serves to differentiate jaundice arising in this fashion from jaundice produced by stone in the common duct. In cases of neoplastic obstruction of the common bile duct, jaundice is usually so intense and the staining of tissue so diffuse that small amounts of bile may reach the intestine from its bile-stained mucosa. Traces of urobilinogen arising from this source can be detected in the stool by

TABLE 3.—*Estimations of Urobilinogen as a Measure of Erythrocytic Destruction*

Case No.	Patient	Diagnosis	Urobilinogen, Mg. per 100 Cc. of Urine	Bile in Urine	Urobilinogen, Mg. per 100 Gm. of Stool	Icterus Index
35	M. C.	Congenital hemolytic anemia.....	28.0	++	2,625.0	26.6
36	A. T.	Congenital hemolytic anemia.....	No increase	Absent	675.0	32.6
37	G. S.	Pernicious anemia	No increase	Absent	869.0	16.0
38	G. K.	Malaria	12.0	+	634.0	17.0
39	F. A. R.	Anemia following sulfanilamide therapy	59.2	+++	1,133.0	35.0
40	G. H. S.	Aplastic anemia	No increase	Absent	56.7	8.0

Watson's method. With my method, however, the amount of urobilinogen formed is insufficient to yield a positive result. In case of jaundice due to stone, some urobilinogen can almost invariably be demonstrated in the stool or urine at some time.

In each of the 5 cases in my series it was possible to make a diagnosis of neoplastic obstruction of the common bile duct by observing persistent absence of urobilinogen from the stool over a period of at least seven days. Urobilinogen reappeared in the stool in normal amounts and in the urine in greatly increased quantities after surgical establishment of a new channel for passage of bile into the intestine.

Three cases of partial obstruction of the common duct were observed. In 1 case obstruction was caused by stricture which followed exploration of the common duct (case 33). In case 34 severe intermittent jaundice of several weeks' duration resulted from an anomalous vessel which crossed and occluded the common bile duct; the jaundice subsided promptly after ligation of the vessel. In case 32 the obstruction was caused by a stone in the common bile duct. After relief of the

obstruction increased amounts of urobilinogen appeared in the urine, gradually diminishing as the patient improved.

It has previously been stated that any condition which causes obvious clinical jaundice of moderate or severe degree is associated with sufficient hepatic damage to cause pathologic urobilinogenuria, if bile is reaching the duodenum. For example, with neoplastic obstruction of the common bile duct the associated biliary cirrhosis is sufficient to cause increases of urinary urobilinogen were it not for the fact that the obstruction prevents bile from reaching the intestine. One may therefore expect increases of urobilinogen to follow surgical or spontaneous relief of complete or partial obstructions of the common duct.

In employing determinations of urobilinogen in the differential diagnosis of jaundice it is essential that repeated analyses be made for several days. The urobilinogen findings during the obstructive phase of acute intrahepatic jaundice are similar to those associated with neoplastic obstruction of the common bile duct, and diagnosis of the latter can be made with certainty only when it has been demonstrated that the obstruction has existed for at least a week. By repeated estimations in cases of acute intrahepatic jaundice it is often possible to predict the subsidence of jaundice before it is manifest clinically or is indicated by a fall in the icterus index.

C. ESTIMATIONS OF UROBILINOGEN AS A MEASURE OF DESTRUCTION OF RED CELLS

Estimation of urobilinogen in the measurement of destruction of red cells is largely confined to the stool. In cases of uncomplicated hemolytic disease the liver is capable of disposing of large excesses of bilirubin, so that greatly accelerated erythrocytic destruction can occur without associated increase in urinary urobilinogen. It is frequently observed, however, that in cases of severe hemolytic disease there is considerable increase of urobilinogen in the urine. This has been variously explained as due to complicating hepatic damage or to simple overflow of excessive urobilinogen through the liver. Watson expressed himself in favor of the former view.[8d]

The 6 cases in this group consist of 5 instances of anemia of increased destruction of red cells and 1 of decreased production. In 2 cases of congenital hemolytic anemia, 1 case of malaria, 1 case of pernicious anemia and 1 case of anemia which followed sulfanilamide therapy there were increases of fecal urobilinogen above the normal range. In 1 case of aplastic anemia the urobilinogen of the stool was below the normal range.

In 3 cases of hemolytic disease (cases 35, 36 and 38) increase of urinary urobilinogen was also noted. In each instance in which this increase was observed bile pigment was also detected in the urine.

COMMENT

In the present study the series of cases, although small, demonstrates conclusively that information of value may be obtained from the examination of single specimens of stool and urine according to the method described.

By this method it is possible to detect hepatic damage and to follow its course. Differentiation can be made between jaundice of intrahepatic origin and that arising from obstruction to the extrahepatic biliary passages. The importance of this differentiation in recognition of conditions which require surgical intervention is obvious. Neoplastic obstruction of the common bile duct can usually be differentiated from other causes of obstruction by the persistent absence of urobilinogen in the stool. The rate of destruction of red cells can be estimated, and differentiation between anemias of increased destruction and those of decreased production is aided. The method affords a means of detecting significant hepatic damage which accompanies acute or subacute disease of the gallbladder.

In working with the stools of patients with complete and partial occlusion of the bile ducts it has been forcibly impressed on me that little idea as to the amount of bile pigment derivatives which the stool contains can be obtained from observation of its color. Completely acholic stools frequently have considerable color, derived either from ingested material or from blood. Chemical analysis is essential if any accurate idea is desired regarding the amount of pigment in a stool.

Utilization of a sensitive test for bile pigment has demonstrated that significant increases of urinary urobilinogen are always accompanied by the presence of detectable quantities of bile pigment in the urine.

Rich [11] made a broad subdivision of jaundice into the retentive and the regurgitant type. The former type arises as a result of increased destruction of red cells with retention of excesses of bile pigment in the blood stream and is characterized by absence of bile pigment from the urine. The regurgitant type arises from regurgitation of whole bile into the blood stream and is produced by disease of the liver or obstruction of the bile passages. The bile pigment entering the blood in such cases is more diffusible and is capable of passing the kidney, so that it appears in the urine.

Rich suggested, however, that the ability of the normal liver to dispose of large excesses of bile pigment is so great that it may even be impossible for clinical jaundice to arise solely as a result of increased destruction of red cells; he stated that the appearance of jaundice in such an instance points to hepatic damage and indicates that a regurgi-

11. Rich, A. R.: Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338 (Dec.) 1930.

tant as well as a retentive component of the jaundice has developed. If these theoretic concepts are true, the appearance of obvious jaundice and of urobilinogenuria should be accompanied by the appearance of bile pigment in the urine, since this finding is characteristic of regurgitant jaundice. By the sensitive method employed in my series bile pigment was demonstrated in the urine of every patient who had pathologic urobilinogenuria.

Thus the finding of bile pigment and urobilinogen associated in the urine in certain cases of hemolytic jaundice lends support both to the ideas of Rich regarding the pathogenesis of the various forms of jaundice and to Watson's belief that pathologic urobilinogenuria occurs in hemolytic processes only when there is complicating damage to the liver.

It is no doubt true that in cases of borderline hepatic damage or during slight deviations from the normal balance between production and destruction of red cells additional information may be gained from the use of more delicate methods for the estimation of urobilinogen or from the analysis of specimens collected over longer periods. For general diagnostic use, however, the method described has proved highly satisfactory.

SUMMARY AND CONCLUSIONS

The method previously described for determinations of urobilinogen in stool and urine is applicable to routine clinical use.

Valuable clinical information can be obtained from examination of single specimens of urine and stool.

Such estimations of urobilinogen are of value in detecting and following the progress of hepatic damage. This is especially true in cases of abscess of the liver, portal cirrhosis or significant hepatic damage accompanying acute and subacute disease of the gallbladder.

Determinations of urobilinogen are of value in the differential diagnosis of jaundice. Differentiation can usually be made between jaundice of intrahepatic origin and that arising from obstruction of the extrahepatic biliary passages. In the latter condition it is usually possible, by means of studies on urobilinogen, to distinguish between obstructions of the bile passages due to neoplasm and obstructions arising from other causes.

Determinations of urobilinogen in the stool by my method afford an index of the rate of erythrocytic destruction and aid in the differentiation between anemias of increased destruction and anemias of decreased production.

Increases of urinary urobilinogen are consistently associated with the presence of bile pigment in the urine, which indicates that pathologic urobilinogenuria does not occur from excessive destruction of red cells unless there is concomitant hepatic damage.

PANCREATIC CARCINOMA

A REVIEW OF THIRTY-FOUR AUTOPSIES

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Carcinoma is the most common tumor of the pancreas. Its incidence has been cited as from 1.76 to 2 per cent in cases of cancer in which autopsy was done.[1] The types of carcinoma vary considerably in histologic appearance and manner of growth. Three main categories are recognized as representing duct, acinar and "islet" structures.[2] Rarer types, such as mucoid, colloid or squamous (duct) forms, were not seen in this series.

As with cancer situated elsewhere, the causes are unknown. In view of the complex origin of the mature pancreas, which involves anatomic and functional fusion of two separate (dorsal and ventral) duct systems (Wirsung and Santorini), the possibility of developmental errors may be of some importance. This supposition is further supported by the frequency with which carcinoma occurs in the head of the pancreas and the preponderance of the duct type. To this evidence must be added the unstable, constantly regressing and reforming structure of the pancreas, with recurrent waves of loss and hyperplasia of tissue.[3] But all such considerations remain at present speculative as regards development of cancer.

Of particular interest in these cases are associated lesions. Thus, anatomic evidence of chronic irritation is commonly observed in these parts of the pancreas uninvolved by carcinoma. This takes the form of an increase in stroma, either local, about the tumor, or more diffuse, throughout the whole gland. It is probable that this is, in at least a number of cases, an effect produced by the presence of tumor in the

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From the Pathological Institute, McGill University; Prof. Horst Oertel, Director.

1. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 746.

2. In this communication the term "islet," as applied to cells or structures, denotes simply morphologic resemblance to islet cells of the pancreas; it does not refer to a definite or distinct entity. Indeed, the term in these cases cannot always be strictly applied as indicating types distinct from duct forms.

3. Oertel, H., and Anderson, C. M.: Regressive and Progressive Changes in the Pancreas, Scientific Reports, series B, no. 1, Royal Victoria Hospital, Montreal, 1916, p. 163.

organ and not a previously existing lesion or factor conducive to the development of carcinoma. It is not uncommon to note several independent tumor masses in a single organ.

When the main duct has been obstructed by a tumor, small cystic dilatations, hyperplasia and neoplasia are occasionally observed in the ducts proximal to the obstruction. Carcinoma has been observed arising in or about the wall of a larger, previously formed pancreatic cyst.

In the present series of 34 cases of primary cancer of the pancreas in which autopsy was done at the McGill Pathological Institute over a period of twenty years, 26 of the patients were men and 8 women, a ratio of 3.25 : 1. The age distribution was as follows: In 2 cases the condition occurred in the fourth decade of life; in 7, in the fifth; in 10 each, in the sixth and seventh; in 4, in the eighth, and in 1, in the ninth.

GROSS PATHOLOGIC EXAMINATION

Distribution of the Tumors.—In 15 cases the head alone was involved by a single tumor mass except in 1 instance, in which there were several small nodules confined to the head. The whole pancreatic gland was studded with tumor tissue in 11 cases. In 8 of these there were a larger mass in the head and smaller nodules scattered throughout the body and the tail. In 2 instances the entire gland was replaced by the tumor, so that no normal portions of pancreatic tissue were identified. In 1 case the whole gland was diffusely involved by smaller foci of tumor growth. The head and body together were the site of tumor formation in 3 cases. Two of these growths were single large masses, and the third was composed of multiple tumor nodules. The body and tail were similarly involved in 3 cases; in 2 of these the tumor was a single large mass and in 1 it was composed of multiple nodules. The body alone was involved in 2 instances by a single mass of tumor tissue.

Size, Shape and Consistency.—The size of the primary tumors was variable. The largest measurements of single masses ranged from 1.5 to 11.5 cm. Multiple tumor masses varied from the size of a pinhead to 3 cm. in the greatest dimension. In some instances microscopic foci of cancer formation were later detected.

Size and shape bore no relation to origin of tissue. Some tumors were large, ovoid and well demarcated; others were large and fused to the surrounding parenchyma. Some appeared as retracted, firm, scarified areas. Smaller nodules were frequently apparent only on palpation. Some tumors were centrally placed, while others bulged from the surface of the organ.

In general these tumors were firm and hard. A few felt soft or cystic. Cut surfaces were usually a pale homogeneous yellowish gray or white. Some contained softer areas, also seen in their metastases,

from which could be scraped a milky substance. Others had small areas of hemorrhage and necrosis. In 1 case the tumor arose in the wall of a large pancreatic cyst.

Pancreatic and Bile Ducts.—When blockage of the pancreatic duct had occurred by pressure or invasion of the tumor in the head, the proximal portion was usually tortuous and dilated with a milky or watery fluid. Many small cystic dilatations were seen throughout the length of such ducts. Frequently the pancreatic tissue proximal to the obstruction appeared atrophied or collapsed or felt soft. Pancreatic calculi were not noted in any of the cases.

The common bile duct was obstructed in 12 and compressed in 8 instances. In these cases 6 tumors were in the head; 10 involved the whole gland, and 1 occurred in the body with extension into the head. In 3 cases lymph nodes in the gastrohepatic ligament caused pressure on the common bile duct. Stone in the common duct was observed in only 1 case, and in this it was associated with obstruction by a lymph node.

Extensions and Metastases.—There appeared a definite tendency in these tumors first to adhere to adjacent structures and then to infiltrate them. Coaptation was brought about by enlargement of the part of the organ involved by tumor or by direct infiltration and contraction of intervening tissues. This tendency to stimulate formation of abundant stroma and connective tissue within the tumor, the organ and the surrounding tissues has been spoken of as a desmoplastic property of pancreatic carcinoma.

Gastrointestinal Extension: Local extensions, excluding involvement of lymph nodes, occurred in 18 cases. The pylorus of the stomach was adherent in 8 instances. In 3 of these cases there was gastric ulcer with metastatic invasion, and in 1 the wall of the stomach was invaded, the mucosa being left intact. In 2 other cases gastric ulceration occurred without metastases or adhesion. The duodenum was adherent in 10 cases. In 3 of these there was duodenal ulceration with carcinomatous invasion. In 6 cases the tumor invaded the duodenal wall, leaving the mucosa intact, and in 1 case there was simple adhesion to the tumor mass. In the cases in which there was carcinomatous ulceration of the gastrointestinal tract, the gross appearance of raised thickened edges and radiating rugae suggested previously existing peptic ulceration with secondary carcinomatous invasion. The tumor was adherent to the transverse colon in 4 instances and had invaded its outer coats in 1 case. The descending colon was invaded by peritoneal metastases in 2 cases, in 1 of which the bowel was partially obstructed without ulcerating.

Metastases to Peritoneum: Peritoneal seeding occurred in 8 cases. In 2 of these the nodules were localized to the region about the tumor, while in the remainder multiple and single nodules were observed in

more remote parts of the abdomen, including the cul-de-sac (3 cases). Ascites was found in 3 of the 8 cases.

Metastases to Lymph Nodes: This involvement was frequent. Regional nodes (gastrohepatic and pancreatic) contained metastases in 28 instances. Retroperitoneal lymph nodes about the abdominal aorta were involved in 15 cases. Extension into the nodes of the mesentery occurred in 11 cases, and metastasis to the mediastinal and peribronchial lymph nodes was observed in 8. The supraclavicular nodes were involved in 3 instances, in 1 on the right, in 1 on the left and in 1 bilaterally, and the inguinal nodes in 4 cases, in all on the right.

TABLE 1.—*Distribution of Metastases in Thirty-Four Cases of Primary Carcinoma of the Pancreas* *

Organ	No. of Cases
Regional lymph nodes	28
Liver	25
Para-aortic abdominal lymph nodes	15
Mesenteric lymph nodes	11
Lungs	10
Mediastinal lymph nodes	8
Peritoneum	8
Duodenum	8
Adrenals	7
Skeleton	7
Kidneys	6
Omentum	4
Spleen	4
Inguinal lymph nodes	3
Stomach	3
Intestines	3
Supraclavicular lymph nodes	3
Central nervous system	3
Thyroid	2
Subcutaneous tissue	2
Skeletal muscle	2
Gallbladder	2
Pleura	2
Myocardium	1
Esophagus	1
Pericardium	1

* In 3 cases no metastases were observed.

Metastases to Liver: The liver exhibited metastases in 25 of the 34 cases of pancreatic carcinoma. With 1,300 to 1,800 Gm. as a normal range of hepatic weight and with allowance for variation in the size of individual subjects, the weight of the liver was increased in 12, decreased in 7 and normal in 6 of the 25 cases. In this connection the distance of the hepatic border below the costal margin was not consistent with the weight of the organ. In several instances an apparently enlarged liver, with its anterior border well below the costal margin, actually weighed less than normal. This may have been due to traction on the gastrohepatic ligament, brought about by adhesive and contractive processes in the region of the tumor and its local extensions, or to actual ptosis

of the organ. The majority of livers containing metastases were smooth and firm. Metastases were usually small and multiple and did not bulge the capsule. Ten of the 25 patients with hepatic metastases showed no jaundice, while jaundice occurred in 5 in the series without metastases to the liver.

Jaundice.—Of the 20 patients exhibiting jaundice, 15 had obstruction of the common bile duct by compression or invasion of the tumor; 3 had compression of the duct by enlarged nodes in the gastrohepatic ligament, and 2 had patent ducts. Both of the latter exhibited metastases in the liver; 1 of them had thrombosis of the portal vein, and the other, thrombosis of the inferior vena cava. In no other case did thrombosis occur in vessels directly related to the hepatic circulation. It seems therefore that thrombosis in the afferent or efferent veins of the liver is a factor in the production of jaundice. Metastases to the liver apparently play a minor part in the production of jaundice, except when main hepatic ducts become obstructed by metastases near the hilus or when there is massive replacement of liver by tumor tissue. Both of these events are rare.

Effects of Biliary Obstruction.—All of the 18 patients with obstruction of the common bile duct showed dilatation of the intrahepatic and extrahepatic biliary tree of varying degree. Similarly, the gallbladder was seen to be dilated either at operation or post mortem. Three patients had associated productive cholecystitis, 2 with cholelithiasis. In all cases the gallbladder and duct bile were of normal color and consistency, except in a case of gallstones in which the thickened gallbladder was tensely dilated with pale mucoid material.

Evidence obtained from clinical, operative and postmortem examinations suggested in most instances the following sequence of events with respect to hepatic enlargement: With the onset of biliary obstruction the gallbladder and the extrahepatic and intrahepatic bile ducts dilate, and the liver gradually enlarges. In the course of time progressive atrophy of the hepatic parenchyma supervenes. This sequence of events seemed well illustrated in a case in which the liver, with metastases, weighed at autopsy only 750 Gm., although it had been palpably enlarged during life and was noted as "enlarged" during operation (cholecystogastrostomy), three weeks before death. Generally, however, when metastases were numerous the liver remained enlarged (over 2,000 Gm. in 8 cases).

Ascites.—Ascites was present in 8 cases. Peritoneal metastases associated with ascites occurred in 3 instances. Other reasons for ascites appeared to be partial obstruction of the venous return, portal and caval, by enlargement of lymph nodes, hepatic metastases and portal thrombosis. In 1 case definite peri-insular cirrhosis of the liver

was associated with ascites. In another case there was chylous ascites from massive tumor invasion of lymph nodes in the region of the diaphragmatic crura. The ascitic fluid was usually pale yellow and cloudy and occasionally blood tinged.

Edema.—Edema of the lower extremities occurred with ascites in 5 instances. Swelling of the feet and legs, unilateral or bilateral, occurred independently of ascites in 5 cases. In 3 of these thrombosis of the femoral or iliac veins was demonstrated, with extension into the inferior vena cava in 2 instances. Metastases to the right inguinal lymph nodes were responsible in 1 case and peritoneal metastases in the left lower quadrant in another.

Metastases to Skeletal and Central Nervous Systems.—Skeletal metastases occurred in 7 cases. The spine and ribs were involved in 3 cases, the clavicle in 2 and the skull, sternum, scapula, ilium, sacrum and femur in 1 instance each. Growths in the vertebrae caused pressure on the cord. The central nervous system showed metastases in 3 instances. The brain and the dura were involved in 2 cases and the longitudinal sinus and the spinal cord in 1.

MICROSCOPIC EXAMINATION OF PANCREAS

Pancreatic Invasion.—The manner of expansion and invasion of these tumors within the pancreas deserves mention because of the possibility of mistaken diagnosis due to bizarre formations and degrees of distintegration and collapse in the tissue adjacent to the tumor. Such sections revealed an increase of stroma, with varying degrees of collapse of parenchyma and dilatation of intralobular ducts and acini and breaking down of acini and smaller ducts into single or small groups of cells. In these fields there was a distinct tendency for islet cells to remain conspicuous. Thus, typical duct carcinoma or acinar carcinoma will in the cirrhotic environment of the periphery alter the normal structure of ducts and acini to the appearance of new growth, although in reality no actual tumor has overgrown these parts.

The picture produced in individual lobules was not unlike that seen in the proximal portion of the pancreas in some instances in which the main pancreatic duct was obstructed. Complete pathologic obstructions of the duct in the head or body eventually lead through atrophy and collapse to total disappearance of acini and lobular structure, with increase of stroma and prominence of islet tissue about larger dilated ducts in the proximal parts of the gland (fig. 1). It appears that local expansion of cancers within the pancreas leads to strangulation or obstruction of the efferent ducts of individual lobules, with resultant loss of acini and proliferation of stroma. This possibility is further supported by the appearance of dilated acini and ducts within lobules in earlier stages of invasion of adjacent tissues.

Sections frequently showed an apparent increase in larger interlobular ducts, which were surrounded by increased stroma, in some instances resembling foci of carcinomatous duct growth. Closer inspection revealed that this growth was only apparent, being the result of atrophy, collapse or total loss of lobules. In some instances, however, in which partial obstruction had evidently persisted longer, there was definite papillary hyperplasia, particularly in larger dilated ducts. In 1

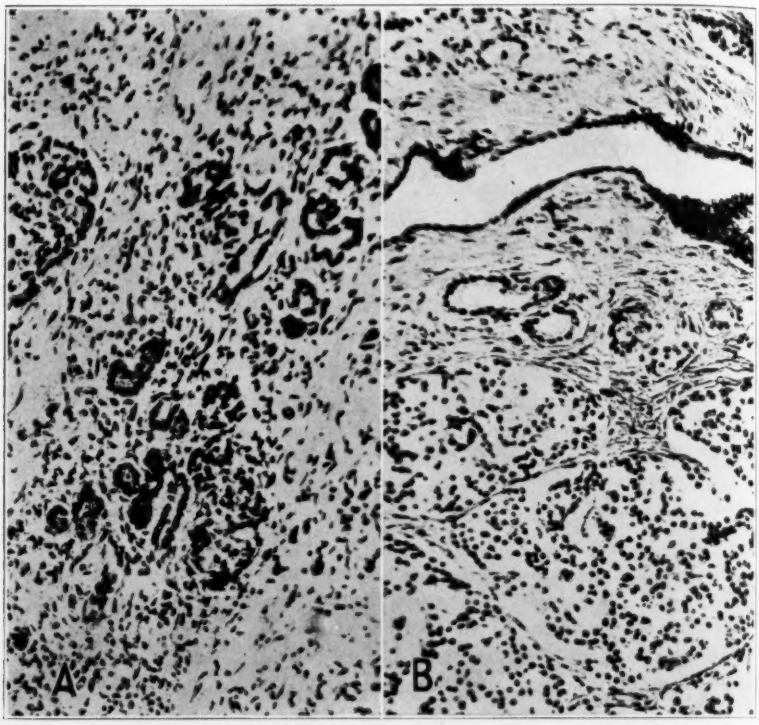

Fig. 1.—*A*, effect of the tumor on adjacent pancreatic tissue. *B*, result of obstruction of the pancreatic duct. Note the total loss of acini and of the lobular structure and prominent islet tissue about the larger ducts.

instance this had gone on to neoplasia, with the formation of an intraductal papillary adenoma in the tail (fig. 2).

Characteristics of Tumors.—Of the 34 tumors, 25 were of the duct, 7 of the acinar and 2 of the islet type of carcinoma. The duct cancers showed an excessive amount of stroma as compared with the other types. These varied slightly, but all exhibited distinct duct formation.

regardless of whether the tendency was to grow in solid or in alveolar fashion. The size of the ducts, the height of the lining epithelium and the tendency to papillary growth were all variable. Cell types ranged from tall columnar to low cuboidal and from pale mucoid to deeper-staining, finely granular cytoplasmic. Thus, cell types and arrangements emulating intralobular, extralobular and main ducts were seen in this group (fig. 3).

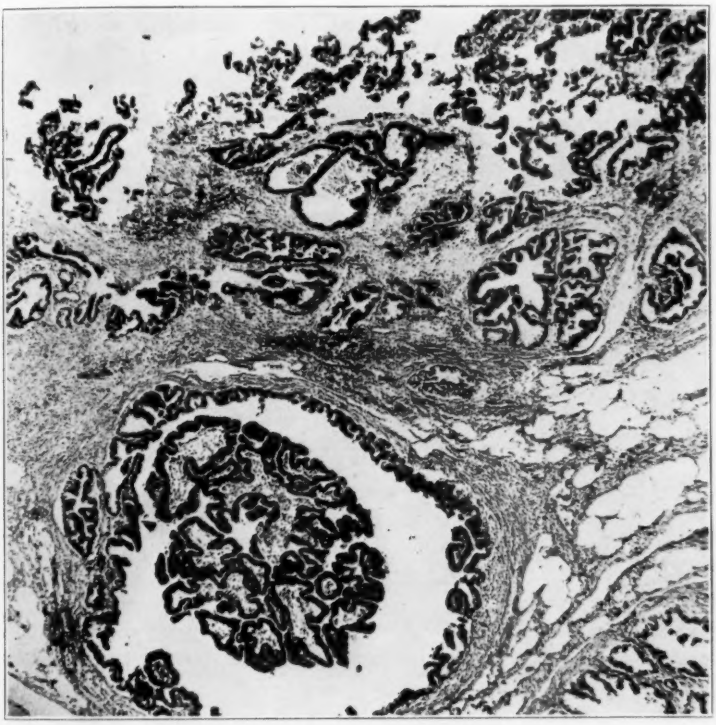

Fig. 2.—Papillary hyperplasia with obstruction of the main duct. Note the adenoma formation and the collapse of surrounding parenchyma.

The 7 acinar carcinomas all grew as solid masses of cells, with little stroma between cells. Larger cell masses were separated by more definite fibrous cords. These tumors had a distinct, solid diffuse or solid alveolar manner of growth. Only at the periphery of such tumors were ductlike structures suggested in the breaking down lobules. There was a greater tendency to tumor necrosis in this group. Cell types varied more than in the other two varieties of carcinoma. Polyhedral

cells, small round cell types and even elongated, spindle-like shapes were seen (fig. 4).

The 2 islet carcinomas showed a distinctive manner of growth closely resembling the islet adenomatous structure. The presence of metastases and local invasive properties, however, indicated the cancerous nature of these tumors. In places they exhibited a tendency to grow in more solid cell masses, and in others a tendency to duct forma-

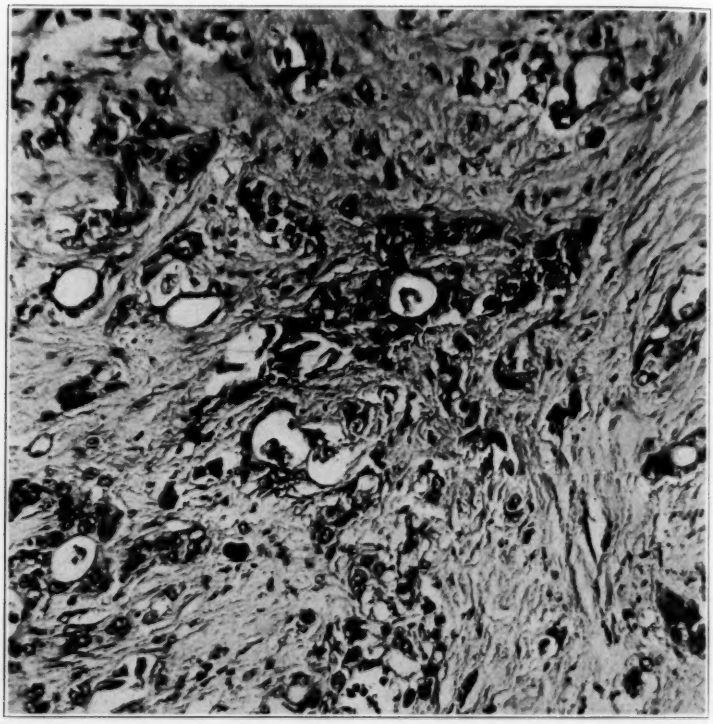

Fig. 3.—Typical duct carcinoma. Note the abundant scirrhous stroma, the abortive duct formations and the cell masses.

tion was noticeable, but with cell types characteristic of islet tissue. These peculiarities are explicable on the basis of origin of islet tissue from intercalary ducts and centroacinar cells (fig. 5).

Relation of Pancreatic Carcinoma and Blood Sugar.—Determinations of blood sugar were made during the course of the disease in 14 cases (table 2). With the upper normal limit of the level during fasting

as 120 mg. per hundred cubic centimeters and the upper normal limit for the postcibal level as 150 mg., in this group of 14 cases there were 8 instances of a raised sugar level, 5 cases of a level within normal limits and 1 instance of a decreased postcibal level. Sugar tolerance tests were made in cases 21 and 32. In the former a normal curve was exhibited, and in the latter a decreased tolerance curve of the prolonged, raised type.

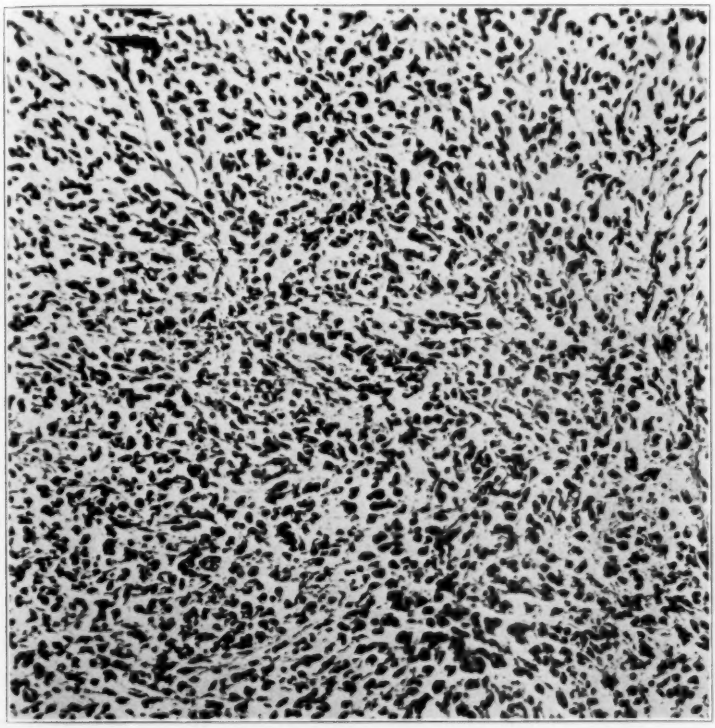

Fig. 4.—Typical acinar carcinoma, showing pleomorphous cell types and a diffuse manner of growth.

No correlation could be established between altered sugar levels and the hepatic weight, metastases to the liver, obstruction of the common bile duct or metastases to other organs known to have a physiologic effect on the blood sugar level. Stains for glycogen granules of the liver (Best's carmine method) revealed that they were decreased and confined to the periphery of the lobules.

The changes in the pancreas showed the most consistent correlation with the blood sugar level. Unfortunately, studies on sugar were not made in the 2 cases of single islet cancer. It appears, however, that both the duct and the acinar type of carcinoma exhibited associated effects on the blood sugar level. Nevertheless, in 5 cases in this group the blood sugar range was normal. It appears therefore that the effect, if any, produced by carcinoma of the pancreas on the blood sugar level

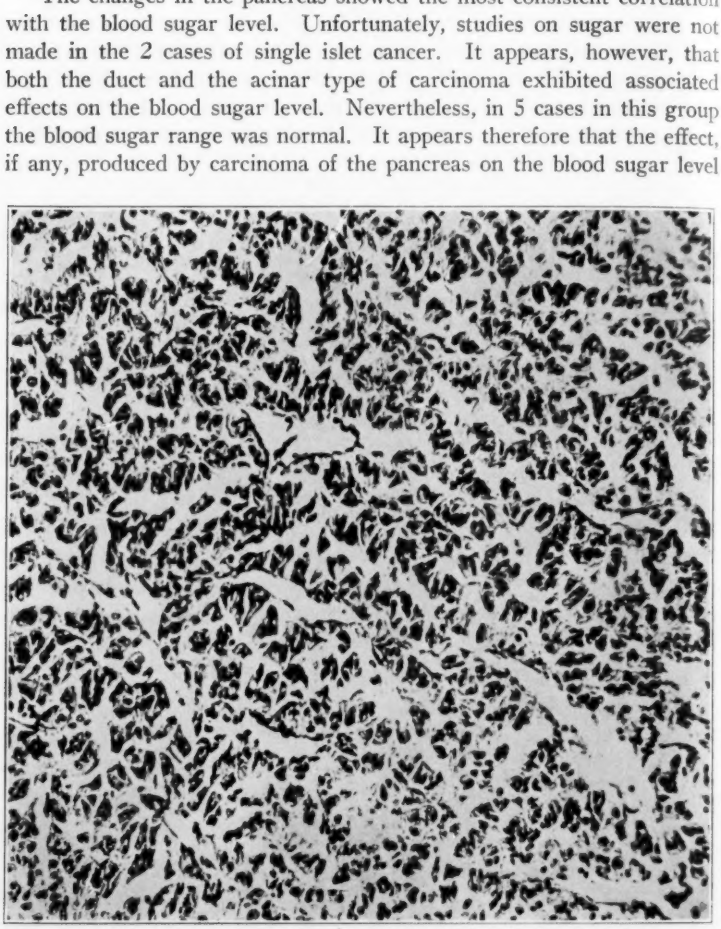

Fig. 5.—Islet carcinoma, showing cells arranged about vascular spaces.

must be due not to the type of tumor but to the effect of the tumor on the rest of the pancreatic gland. When the pancreas has been totally replaced by tumor growth, when massive collapse of pancreatic tissue has occurred proximal to tumor obstruction of the main pancreatic duct or when diffuse fibrosis has led to extensive loss of parenchyma, a disturbance in blood sugar levels is almost uniformly assured.

Sections from the parts of the pancreas which were not involved in actual tumor growth all showed relatively well preserved islet tissue.

Various degrees of lobular atrophy and loss of acini and intralobular ducts were noted in all cases in which blood sugar levels were disturbed. In the cases of most severe involvement, in which there occurred the equivalent of ligation of the pancreatic duct, there was total collapse of acini and of the lobular structure, with groups of islands arranged about dilated extralobular ducts. In several cases there appeared diffuse increase in perilobular connective tissue, which in some instances grew diffusely throughout the lobules. In these instances there was associated loss of acinar tissue, and the picture was not unlike that seen in hepatic cirrhosis.

Definite conclusions cannot be drawn, nor can a hypothesis be established, on the basis of the present analysis. That the control of blood sugar levels is not entirely localized in the pancreas is shown by

TABLE 2.—*Blood Sugar Levels in 14 Cases of Pancreatic Cancer*

Case No.	Site	Size	Type	Blood Sugar, Mg. per 100 Cc.	
				During Fasting	Post-cibal
5	Head	3 cm. in diameter	Duct	164*	...
6	Head	5 cm. in diameter	Duct	119	144
11	Head	5 cm. in diameter	Duct	131*	...
13	Head, body and tail	Half of head free	Acinar	133*	...
17	Body and tail	7 cm. in diameter	Duct	372*	369*
21	Head, body and tail	Multiple nodes	Duct	99	141
23	Head	Multiple nodes	Duct	97	136
26	Body and tail	Multiple nodes	Duct	102	185*
28	Body	11 by 5 cm.	Acinar	105	163*
30	Head and body	8 by 4 cm.	Duct	200*	...
32	Head, body and tail	Multiple nodes	Duct	102	174*
33	Head	2 cm. in diameter	Duct	...	147
24	Body	8 cm. in diameter	Duct	...	120
10	Head, body and tail	Multiple nodes	Duct	...	72

* Level abnormally high.

the effects produced on sugar values by pathologic lesions in the brain, hypophysis cerebri, thyroid and adrenals. One conclusion may be stated, however, with regard to pancreatic carcinoma other than the islet type. As previously mentioned, the type of carcinoma, duct or acinar, is of less importance in relation to blood sugar values than the effect produced by the tumor on the rest of the pancreatic gland. When loss of parenchymatous substance, and acinar structures in particular, has occurred in the pancreas outside the tumor proper, there is a tendency to a raised blood sugar level and lowered sugar tolerance.

CLINICAL NOTES

In this group of 34 cases of primary pancreatic carcinoma, the earliest symptoms were related to the primary tumor in 28 instances and to metastases in 6.

The earliest common complaint was epigastric pain in 20 cases. This varied widely, ranging from a dull ache to a sharp colicky pain and from an intermittent to a persistent form. The commonest site for radiation of pain was the right upper quadrant of the abdomen and the lower part of the right thorax anteriorly. Only 5 patients had pain in the back during the course of the disease. Pain related to meals occurred in a few instances, beginning anywhere from fifteen minutes to two hours after food was taken. Four patients had a typical history of peptic ulcer, although no gastrointestinal lesion was demonstrable post mortem.

Clinical symptoms of hypoglycemia were not recorded in this series, even in the 2 cases of the more typical islet types. A feeling of fulness, gaseous eructations and general weakness were early common complaints. Anorexia and loss of weight were prevalent, but usually appeared late. Constipation occurred with greater frequency than diarrhea, particularly in jaundiced patients. No anatomic lesions were observed which directly explained the diarrhea. It is assumed that interference with the normal production and flow of digestive ferments was responsible in these instances. In 1 case the duodenal contents were analyzed, and no pancreatic ferments were demonstrable. The color and consistency of diarrheic stools were inconstant.

Nausea and occasional vomiting occurred in 11 instances, but as a rule not as an early symptom. However, in a few cases morning nausea did appear early. In 5 patients with these symptoms, gastrointestinal lesions were revealed at autopsy. These consisted of nodular extension of the tumor into the duodenum and stomach and adhesions to the pylorus, duodenum and transverse colon. In some ulceration was associated with metastases.

Gastric analyses were made in 12 cases. In 7 there was no free hydrochloric acid. In only 1 case of this group was a gastric lesion revealed at autopsy; this was an ulcer with metastatic invasion. No correlation could be established between achlorhydria and hepatic weight, metastates to the liver or gross gastrointestinal lesions.

Onset of jaundice without pain occurred in only 3 cases, in all of which epigastric pain subsequently appeared. Jaundice occurred in 20 of the 34 cases; in 6 it appeared early, in 5 about midway and in 9 late in the course of the disease. Once established, it persisted in all cases.

Fulness in the upper part of the abdomen, excluding that due to ascites, was frequently observed. Many patients had tenderness with some resistance in the epigastrium and in the right upper quadrant. The liver was palpable in 15 cases, the gallbladder in 7 and the spleen in 3, and masses were felt in other abdominal sites in 2. Clinically, the

Bard-Pic syndrome [4] (distention of the gallbladder, absence of hepatic enlargement, jaundice and rapid cachexia) was the exception rather than the rule in early stages. This syndrome was more frequently observed post mortem. Peritoneal metastases were palpated by rectum in 3 instances.

More frequently hypochromic anemia developed late rather than early. The white cell count usually showed slight neutrophilic leukocytosis with relative lymphopenia and monocytosis. Velocities of sedimentation were usually accelerated.

Roentgen examination with barium sulfate given orally or by enema revealed abnormalities in most, but not all, cases in which lesions involving the gastrointestinal tract were demonstrated at autopsy. In other instances, when roentgen studies gave negative findings, the gastrointestinal tract was uniformly normal post mortem. The commonest roentgen finding was gastric delay. A few patients showed irregularities or deformities in the outline of the stomach or duodenum; very few had colonic filling defects in the transverse colon where peritoneal metastases had caused narrowing of the lumen.

The 6 patients whose earliest symptoms were related to metastases uniformly had pain in the legs, hips or arms, sometimes of sciatic nature and usually unilateral. In 3 instances this progressed to sensory or motor paralysis or to both. Metastases to the skeleton were demonstrated in 5 of the 6 cases and to the dura or brain in 3 instances. In 1 patient ulnar paralysis had developed from pressure of lymph nodes in the supraclavicular fossa on the brachial plexus.

There was wide variation in the duration of the disease as measured from the onset of the earliest symptoms until death. In 2 instances complaints began five and seven years, respectively, prior to the patient's demise. In 2 patients the course extended over a period of three years and in 2, over two years. The remaining 28 patients died within a year of onset of symptoms, as follows: Four lived one to two months; 5, two to three months; 4, three to four months; 4, four to five months; 2, five to six months; 1, six to seven months; 5, seven to eight months, and 1 each, nine, ten and eleven months. It is thus seen that the illness may be sudden and acute or gradual and chronic.

SUMMARY

Thirty-four autopsies on patients with pancreatic carcinoma are reviewed. The highest incidence occurred in the fifth to the seventh decade, and the condition was present in men 3.25 times as often as in women.

4. Bard, L., and Pic, A.: Contribution à l'étude clinique et anatomopathologique du cancer primitif du pancréas, Rev. de méd., Paris **8**:257, 1888.

There were 25 instances of duct carcinoma, 7 of the acinar and 2 of the islet type. Fifteen of the 34 patients had multiple tumor nodules in the pancreas. Obstruction of the pancreatic duct by tumor with collapse and fibrosis of the parenchyma was frequently observed. In a few cases the whole gland was almost completely replaced by carcinoma or was diffusely fibrotic with loss of parenchyma.

The effect on blood sugar levels bore no relation to the type of cancer. In the cases of islet cancer, determinations of sugar levels were not available, but no symptoms of hypoglycemia were recorded. The amount of damage caused by the tumor to the pancreas as a whole did show a relation to sugar levels. There was a general tendency to a raised blood sugar level and lowered sugar tolerance when loss of parenchyma was extensive.

Metastases and other postmortem observations are discussed.

Some clinical observations on pancreatic carcinoma are noted and correlated with changes seen at autopsy.

THE BREATH-HOLDING TEST

A SIMPLE STANDARD STIMULUS OF BLOOD PRESSURE

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The patient with essential hypertension has an excessive physical and emotional response to many different stimuli. The study of these excessive responses, especially of the blood pressure, is of great importance in the early recognition of the disease. The use of a simple standardized stimulus (cold) to study the response of blood pressure in cases of essential hypertension was first reported by Hines and Brown [1] in 1932.

In a previous paper,[2] we reported our own results with 313 cold pressor tests, and in general we have been able to confirm the findings of Hines and Brown. During the past year, we have devised and investigated a new standard test utilizing vasomotor stimulus—the breath-holding test—and the following is a preliminary report of our findings with this test:

TECHNIC OF THE BREATH-HOLDING TEST

With the subject sitting in a quiet room, the blood pressure is determined at about five minute intervals until a basal level is obtained. This basal level varies with the severity of the hypertensive disease and the degree of relaxation. The length of the rest period varies from twenty minutes to forty-five minutes and is in general much briefer for the subject with normal blood pressure than for the hypertensive patient. If after twenty minutes of rest in a chair the systolic blood pressure of the hypertensive patient does not drop at least 30 mm. of mercury, even with advanced disease, it is clear to us from past experience that the patient is still tense and that a basal level has not been reached. In such cases either a longer rest period is used or the test is done with the understanding that a basal

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Presented in abstract at a meeting of the New England Heart Association, Boston, March 28, 1938.

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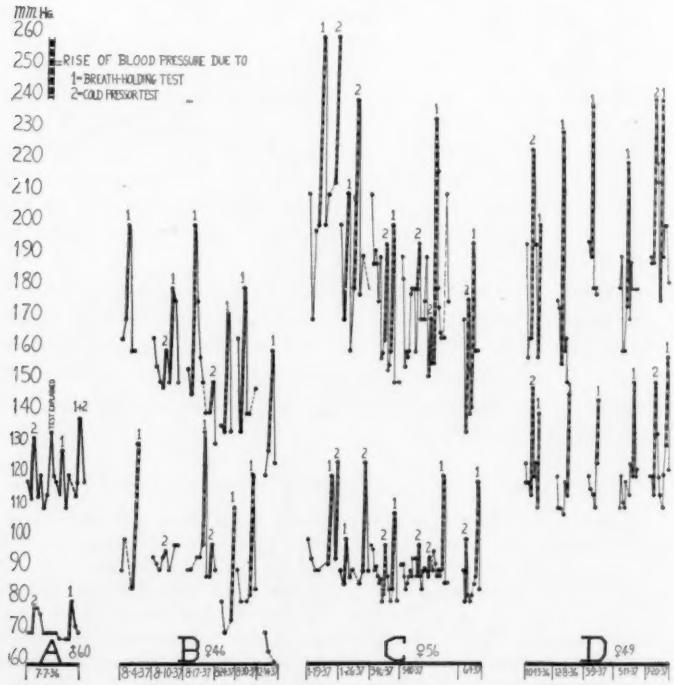
1. Hines, E. A., Jr., and Brown, G. E.: A Standard Stimulus for Measuring Vasomotor Reactions: Its Application in the Study of Hypertension, Proc. Staff Meet., Mayo Clin. **7**:332 (June 8) 1932.

2. Ayman, D., and Goldshine, A. D.: The Cold Pressor Test as a Standard Stimulus of Blood Pressure, New England J. Med. **219**:650 (Oct. 27) 1938.

level was not obtained. That this is true is invariably borne out by subsequent visits, when the patient has become accustomed to the physician and a much lower basal level of blood pressure is obtained. The chart (*C*) illustrates the reactions of the blood pressure of a mildly hypertensive patient, whose basal systolic level was 170 mm. on the first visit, 160 mm. on the second visit and 134 mm. on the sixth visit. For subjects with normal blood pressure, a similar rest period is necessary, but usually the basal level is obtained more quickly. When after an adequate fall of blood pressure and at least twenty minutes of rest, we find that



Blood pressure reactions to (*1*) the breath-holding and (*2*) the cold pressor test. The upper levels of the chart represent systolic and the lower levels diastolic blood pressure. The numerals at the bottom indicate the dates of individual visits of the same subject. The letters *A*, *B*, *C* and *D* refer, respectively, to a subject with normal blood pressure, a hyperreactor and 2 subjects with essential hypertension. A complete break in the lines of the chart indicates the end of each visit.

two or three readings of the blood pressure repeated every few minutes are within 10 mm. of each other, a basal level is considered to have been reached. (The chart [*A*] illustrates the basal readings of a typical subject with normal blood pressure.) The technic of the test is then explained to the subject. This explanation in itself is a stimulus to blood pressure in most persons (chart *A*), so that it must be followed by a few more minutes of rest, till at least the original basal level is again obtained.

The subject is then asked to compress his nostrils suddenly with the fingers of the free hand and simultaneously close the mouth by compressing the lips. He is cautioned in advance and also at the time of the test not to inhale or exhale just prior to the test. Both these points are checked by observation. Actually, the command to close the nose and mouth is given at the observed moment of normal quiet expiration. The subject is told to keep the nose and mouth closed without allowing the slightest amount of air to pass in or out. Further, he is advised that the time of holding the breath is to be twenty seconds, and that the final few seconds are usually attended by discomfort. He is also asked to relax his chest and body. During the last five seconds of the breath holding, the subject is strongly urged to resist the impulse to breathe.

At the beginning of the breath holding, the observer pumps up the manometer to the level of the systolic blood pressure and follows the systolic blood pressure during the twenty seconds of the test. If the systolic blood pressure rises, the elevation is greatest during the last half of the breath holding. At exactly the end of the twenty seconds, as determined by the second hand of an ordinary watch, the final systolic reading is noted; the subject is then told to breathe again, and the blood pressure cuff is deflated. The blood pressure returns to or falls slightly below the original basal level within a minute or two. After a few minutes of rest and a return to the basal level, the test is repeated, but this time at the start of the test the cuff is inflated to the level of the diastolic blood pressure and the rise of diastolic blood pressure followed during the test. Although it is possible to determine both systolic and diastolic blood pressure in the one breath-holding period, the time necessary to read both systolic and diastolic pressure will carry the breath holding beyond twenty seconds and make for greater discomfort for the subject and inaccuracy in the diastolic reading. The separate determinations of the rise in the systolic and diastolic blood pressure constitute together one complete breath-holding test.

RESULTS OF THE TEST

We have thus far carried out 650 breath-holding tests on 150 ambulatory subjects, 55 of whom had normal blood pressure and 95 of whom had essential hypertension. The average age of both the normal and the hypertensive group was 50 years. Except in rare instances and for particular reasons, the subjects had not used sedatives for at least three days before the test. Our criteria of normal blood pressure were readings well below 145 systolic and 90 diastolic during ordinary visits to the clinic, while blood pressures well above 145 systolic and 90 diastolic constituted among other things the criteria of essential hypertension. Using the original grouping of Hines and Brown, we divided our subjects empirically, first, into those with normal blood pressure and those with essential hypertension (table). We then subdivided the normal group as Hines and Brown did, into a so-called hyporeactor group, in which the rise of systolic or diastolic blood pressure did not exceed 22 mm. of mercury, and a hyperreactor group, in which the rise of systolic or diastolic blood pressure exceeded 22 mm. of mercury. We have tentatively used a 22 mm. rise as the upper limit of a normal hyporeaction, on the basis of the experience of Hines and Brown with the cold test.

The table shows the average rise of the blood pressure in the different groups. Forty-six subjects had normal blood pressure at the time of the test, no clinical evidence of previously elevated blood pressure and a reaction to the breath-holding test of less than a 22 mm. rise in either the systolic or the diastolic blood pressure. The mean rise of blood pressure for the group was 11.6 mm. of mercury systolic and 11.7 mm. of mercury diastolic. This low average rise of blood pressure indicates that most of the subjects had rises much less than the upper limit of 22 mm. of mercury. The chart (*A*) represents a typical case.

Nine subjects with normal blood pressure at the start of the test reacted excessively to the test, i. e., with a rise of systolic or diastolic blood pressure of more than 22 mm. of mercury. These were called hyperreactors (chart, *B*). The mean rise of systolic blood pressure was 32 mm. of mercury, and of diastolic blood pressure, 21 mm. of mercury.

Finally, there was the group of 95 subjects with essential hypertension, with varying degrees of hypertension and secondary cardio-

Results of Six Hundred and Fifty Breath-Holding Tests

No.	Subjects	Classification	Mean Rise in Blood Pressure, Mm.	
			Systolic	Diastolic
	Those with normal blood pressure			
46		Hyporeactors (0 to 22 mm. of mercury)	11.6	11.7
9		Hyperreactors (22+ mm. of mercury)	32.0	21.0
95	Hypertensive subjects	Tests made after a good basal level was reached	40.7	25.4
		All tests	31.5	21.3

vascular changes. There were many in whom the blood pressure on adequate relaxation dropped to normal during many visits (chart, *C*) and a large number in whom a persistent severe hypertension was present (chart, *D*). We did not analyze the reactions according to the different degrees of hypertension or secondary cardiovascular change. We did, however, analyze the reactions of the hypertensive subjects according to whether a satisfactory basal level was obtained before the test. First, in all the hypertensive patients, regardless of the degree of reaction or arrival at a satisfactory basal level, the mean rise of blood pressure was 31.5 mm. of mercury systolic and 21.3 mm. diastolic. If we omitted those tests in which a basal level was not obtained, as evidenced by later visits and tests, then the mean rise was 40.7 mm. of mercury systolic and 25.4 mm. diastolic.

The reactions in any given subject in general tend to be reasonably constant in being either of a hyporeactor or of a hyperreactor type. We have been able to determine this fact by repeated tests on most of the

subjects (chart, *B, C* and *D*). However, to obtain fairly constant reactions, it is necessary to note that excitement alone will raise the blood pressure markedly. It is, therefore, clear that the first test may give a markedly greater elevation of blood pressure than subsequent tests, because part of the rise is due to excitement and part of it to the test itself. On the other hand, the reaction may become greater on subsequent visits or tests if a lower and more nearly correct basal level of blood pressure is obtained. A repetition of the test within a few minutes will accustom the patient to the procedure and give results more comparable to those obtained on later visits. On the whole, however, subjects who give marked reactions continue to give abnormal reactions despite repetition on the same or subsequent visits. The effect of excitement is greater in the hypertensive than in the normal subject.

The constancy of the rise in blood pressure following breath holding is dependent also on the basal level of blood pressure obtained just before the test. The closer the basal blood pressure is approached, the greater will be the rise on breath holding. Even when a true basal level seems to be obtained and excitement avoided, we find that there may be a marked difference in reaction at different visits in certain subjects. This we have found to be true previously also with the cold test. However, despite all these variations, the general pattern of blood pressure reaction remains the same.

We have studied also the effect of increasing the breath-holding time beyond twenty seconds. It is found that many subjects, both normal and hypertensive, if able to hold breath much beyond twenty seconds experience an increasing rise of pressure. In the hypertensive subject such increases may go to tremendous heights. In the normal hyporeactor group such rises may be marked but rarely are. On the other hand, there are many normal hyporeactors in whom prolonging the breath-holding time to from forty to ninety seconds results in but slightly greater rise than the twenty second test. Here again the tendency is for the hypertensive subject to have the hyperreaction with prolonged breath holding, as compared with the normal, hyporeacting subject.

COMPARISON OF THE BREATH-HOLDING AND THE COLD PRESSOR TEST

Throughout our study of the breath-holding test we have repeated on each subject the cold pressor test. We have carried out in this way on the 150 subjects a total of 313 cold tests [2] and 650 breath-holding tests. In all cases we have carried out the breath-holding test first, so that we would not be in any way influenced to maintain a slightly longer breath-holding period in an attempt to obtain a result equal to that of the

cold test. On the whole, there has been a striking similarity of reaction with the two tests. By similarity we mean that when the breath-holding test gave a hyperreaction, the cold test usually did the same. In general, however, the breath-holding test gives a greater reaction, although of a similar degree. There have been a number of cases, however, in which the cold pressor test gave little or no reaction and the breath-holding test gave a hyperreaction.

To compare properly the reactions to these tests in a given subject it is necessary to obtain a similar basal level before each test. This, however, is not easy, in hypertensive subjects especially. The blood pressure of such subjects varies so markedly during the course of an hour that it is only in a small number that one can obtain a similar basal level. Of 44 hypertensive subjects in whom we were able to obtain similar basal levels with each of these tests at the same visit, we found a marked similarity of reaction in 28. Fifteen others had a greater rise with the breath-holding test. Three patients in whom there was practically no rise with the cold test had a marked response with the breath-holding test. Of the 44 patients, 37 had hyperreactions to both the breath-holding and the cold pressor test, while 43 had hyperreactions to the breath-holding test. One patient, with "fixed" hypertension and chronic nephritis, whose blood pressure did not drop during the resting period before the test, had a hyporeaction to both the breath-holding and the cold pressor test. On the whole, however, even though the basal level of blood pressure is not precisely the same before each of these tests, we have found in the other hypertensive patients that hyperreactions to both tests occur in most cases.

MECHANISM OF THE TEST

Although breath holding in various forms has been used since the classic experiment of Valsalva, the use of breath holding by the method here described for the determination of its effect on the vasomotor system appears to be new. The test was devised purely on the assumption that since hypertensive subjects seem to be sensitive to all stimuli and among the known stimuli to the vasomotor center is lack of oxygen, or increase of carbon dioxide, hypertension might be diagnosed by application of this stimulus. It appeared to us that simple holding of the breath in normal expiration would increase the carbon dioxide content of the alveolar air and that the increase would be quickly reflected in the blood and the vasomotor center, with a resultant stimulus to blood pressure. We were aware of Raab's [3] experiments, in which he showed

3. Raab, W.: Die Beziehungen zwischen CO_2-Spannung und Blutdruck bei Normalen und Hypertonikern: Beitrag zur Pathogenese der nicht „nephritischen" Hypertonien, Ztschr. f. d. ges. exper. Med. **68**:337, 1929.

that when carbon dioxide is inhaled there is a greater rise of blood pressure in hypertensive than in normal subjects. Therefore, we devised what seemed to us the simplest method of securing carbon dioxide stimulation, the method of breath holding. We have not, as yet, determined whether this is the mechanism of the rise in blood pressure in this test. It is clear that changes in intrathoracic pressure must be considered. However, we have always tried to be certain that the breath was held just after slight and quiet expiration. This should not be associated with abnormal intrathoracic pressure, which would be present if there was a forced inspiration or expiration. However, it must be recognized that during the last few seconds of the twenty second period most subjects become uncomfortable, and that mild squirming may be associated with changes in intrathoracic pressure. This we will attempt to determine. The mechanism appears to be different from that of the cold pressor test, for when we have carried out the two tests at the same time on the same subject we have obtained a summation of effects.

COMMENT

The foregoing statements indicate that the twenty second breath-holding test furnishes an excellent standard stimulus of blood pressure and appears to cause a rise of blood pressure from two to four times greater in the hypertensive subject than in the normal subject of similar age. It causes as great a rise in blood pressure as does the cold pressor test and in many cases a greater reaction. In this respect it appears to be more effective. From the aspect of convenience, it is clearly simpler to carry out and requires no apparatus. It is, therefore, more practical for bedside or office use.

The question of discomfort arises with any stimulation test. We have found that many people consider the cold test extremely painful and almost unbearable. Others have reported acute reactions and much discomfort. We have questioned patients frequently as to the relative discomfort experienced with the cold test and with the breath-holding test; there appears to be an equal division of opinion. It is clear that holding one's breath becomes uncomfortable from the twelfth second onward and that twenty seconds is the average maximum period. It is likewise clear that the test cannot be conveniently carried out on persons who have shortness of breath from any source. The test, moreover, requires some cooperation of the subject, who must obviously not breathe in or out even slightly.

The significance of the breath-holding test is the same as that of the cold test, whatever the value of either may be. From direct studies of families, family histories and the follow-up reports of some hyper-

reactors over a period of time, it has been shown that hyperreaction to the cold test is of some significance.[4] This holds true also for the breath-holding test. The present report is purely in the nature of a preliminary discussion.

CONCLUSION

Holding the breath in quiet expiration, with the nose and mouth closed, for twenty seconds is a simple standard stimulus of blood pressure. Hyperreactors and hyporeactors can be determined by this method. The test is simpler and furnishes a somewhat greater stimulus than the cold pressor test.

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4. Hines, E. A., Jr., and Brown, G. E.: A Standard Test for Measuring the Variability of Blood Pressure, Ann. Int. Med. **7**:209 (Aug.) 1933. Hines, E. A., Jr.: The Hereditary Factor in Essential Hypertension, ibid. **11**:593 (Oct.) 1937.

RENAL CHANGES FOLLOWING ADMINISTRATION OF HYPERTONIC SOLUTIONS

(50 PER CENT SUCROSE, 50 PER CENT D-SORBITOL,* 50 PER CENT DEXTROSE AND 10 PER CENT SODIUM CHLORIDE)

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Because of the widespread use of hypertonic solutions for intravenous administration in modern clinical practice we became interested in the question whether renal damage resulted from the employment of such solutions and, if so, what the nature and extent of this damage might be. In recent years the intravenous administration of hypertonic solutions of dextrose has become increasingly popular. Lately 50 per cent sucrose has gained wide vogue in the treatment of cerebral edema, glaucoma and retention of fluid resulting from a variety of causes.[1] This material has been rapidly replacing the older dextrose solution for this type of therapy.

Helmholz [2] reported on a series of experiments on rabbits given single and multiple injections of 50 per cent solution of sucrose at various intervals and pathologic studies of the kidneys made at intervals of one to seven days after the final injection of the material. Included in his report was 1 case studied clinically in which it is believed that repeated injections of sucrose (for the relief of high intracranial tension due to meningitis) caused a significant depression of renal function. Our consideration of this work was largely motivated by the following wishes: (1) to use more sturdy experimental animals (dogs), since rabbits are notoriously susceptible to renal injury from even slight insults; (2) to control each experiment with biopsy of the kidneys preliminary to the injections; (3) to use doses in experiments with both animals and human subjects which were comparable with the clinical dose now con-

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*Abbott Laboratories supplied this material. The compound d-sorbitol is an alcohol obtained by the reduction of dextrose, is optically dextrorotary and has the following formula: $CH_2OH—(CHOH)_4—CH_2OH$.

1. Jackson, H.: Ann. Surg. **106**:116 (Aug.) 1937.

2. Helmholz, H.: J. Pediat. **3**:144 (July) 1933.

sidered effective and widely employed, rather than the relatively enormous dose which Helmholz gave his rabbits; (4) to test the effects on human subjects both with and without evidence of impairment of renal function.

At the close of the experiments with sucrose our attention was drawn to a new substance, d-sorbitol. It was then decided to make a comparable series of animal experiments with this material in 50 per cent solution. Further to enlarge the scope of this comparison to include the third principal form of sugar now in use for the purposes originally stated, a series of experiments were similarly performed with 50 per cent solution of dextrose. The only other hypertonic solution which is widely injected intravenously is 10 per cent solution of sodium chloride, used in the treatment of peripheral vascular disturbances.[3] Accordingly, the kidneys of the dogs in which this material had been injected were investigated in the same manner as in the other series.

HUMAN EXPERIMENTS

A series of 15 persons with no known renal damage were given 200 cc. of 50 per cent sucrose intravenously in a single dose. The urine and urea clearance of each of these persons were studied before the administration of the sucrose and twenty-four hours after its administration (several hours after the diuretic effect had subsided). In no case was there evidence of marked impairment of renal function. An occasional specimen of urine after the injection showed a 1 plus reaction for albumin or hyaline casts. The urea clearance remained essentially stationary, and in some cases it was increased by 3 to 5 per cent.

After this 5 patients with known renal damage were similarly studied. In these, too, the urine and urea clearance showed no significant changes as a result of the injection of 200 cc. of sucrose intravenously.

ANIMAL EXPERIMENTS

In spite of the essentially negative clinical results of single doses, we were stimulated by Helmholz' report to study the anatomic effects on normal animals. For this purpose 15 healthy dogs were used. Renal biopsy was performed on each, and after a sufficient period of recovery 100 cc. of 50 per cent solution of sucrose was administered intravenously daily for ten to twelve days. Three days after the last injection the dogs were killed and microscopic sections of the intact kidney made. One animal (dog 1) was given injections for fourteen days and was killed seven days after the last injection. Of the 5 dogs, this one showed the most marked changes (table, dogs 1, 2, 4, 3 and 15). Four of these

3. Siebert, S.: Surg., Gynec. & Obst. **61**:214 (Aug.) 1935.

Results of Administration of 50 per Cent Solution of Sucrose to Dogs in Which Previous Renal Biopsy Had Shown No Abnormality

Dog	Daily Dose, Cc.	Duration of Medication, Days	Interval from Start of Medication to Death	Albumin	Erythrocytes in Urine	Casts	Microscopic Diagnosis
1	100	14	21 days	0	0	+ to ++++	Two thirds of glomeruli showed hemorrhagic necrosis; some tubular degeneration and necrosis
2	100	12	15 days	+ to ++	1 to 5	0 to +	One sixth of glomeruli contracted, with associated tubules showing retrogressive changes
4	100	12	15 days	+ to ++	2 to 30	0	Hyperemia; hemorrhages into tuft; early necrosis of tubules having swollen and granular cytoplasm
3	100	10	12 days	+ to ++	5 to 15	0	Few glomeruli showed retrogressive changes; some hemorrhages into glomerular tufts and changes; early degeneration of convoluted tubules
15	100	10	12 days	+ to ++	1 to 3	+ to ++	Tubules essentially normal; no marked changes seen in glomeruli
14	100	8	10 days	++ to +++	3 to 5	Occasional hyaline	Tubules essentially normal; no marked changes seen in glomeruli
5	100	6	8 days	0	0	0	Occasional hemorrhage into glomerular tuft; necrosis and swelling of some of the collecting loops with nuclear degeneration
8	50	12	16 days	0 to +	5 to 7	0	Many glomeruli showed changes varying from hemorrhages into tuft to coagulative necrosis, with pyknosis of cells of glomerulus; tubules in various stages of degeneration
7	50	10	16 days	0	15 to 20	0	Glomeruli showed degenerative changes in capillary walls and capsule; cells of convoluted tubules were swollen with granular cytoplasm
6	100	1	24 hours	0	0	0	Moderate hyperemia of glomerular tuft; proximal and distal convoluted tubules showed intense swelling nearly obstructing tubules; glomeruli were swollen and hemorrhagic
9	100	1	72 hours	0	0	0	Glomerular and interstitial capillary ingestion; tubular cytolysis, granular degeneration, indistinct cell outlines and sloughing of lining epithelium; tubular nuclei swollen, pale and vacuolated
10	100	1	120 hours	0	0	0	Changes in all of cortical area but in patches at varying intensity; all changes moderate (changes similar to those of dog 9, but not as intense)
11	100	1	168 hours	0	0	0	No significant abnormality

5 dogs showed changes in the kidney ranging from scattered areas of hyperemia and slight tubular changes to actual hemorrhagic necrosis of the glomeruli and marked tubular degeneration (fig. 1). Dog 1 showed only casts in the urine. Dog 15 showed no significant anatomic changes. All the dogs showed some urinary changes, mainly loss of albumin and presence of some red blood cells.

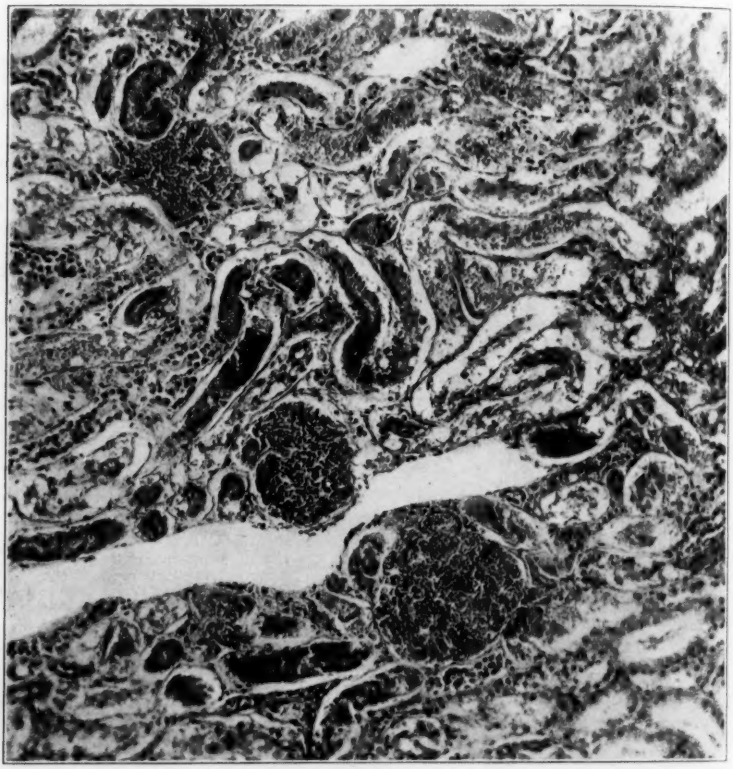

Fig. 1 (dog 1).—Photomicrograph of section of kidney (× 135) removed seven days after the last injection of sucrose, which was given daily for fourteen days. Hemorrhagic necrosis of the glomeruli and marked tubular degeneration can be seen.

After this, 2 more dogs (7 and 8) were similarly subjected to renal biopsy and after recovery were given doses of 50 cc. of 50 per cent sucrose for ten and twelve days, respectively. They were killed six and

four days, respectively, after the last injection (sixteen days after the first injection in each case). The latter (dog 8) showed many glomerular changes, varying from hemorrhages into the tuft to coagulative necrosis with pyknosis and fragmentation of the endothelial cells of the glomerulus. The former (dog 7) suffered degenerative changes in the capillary wall and glomerular capsule, and the tubular cytoplasm was swollen and

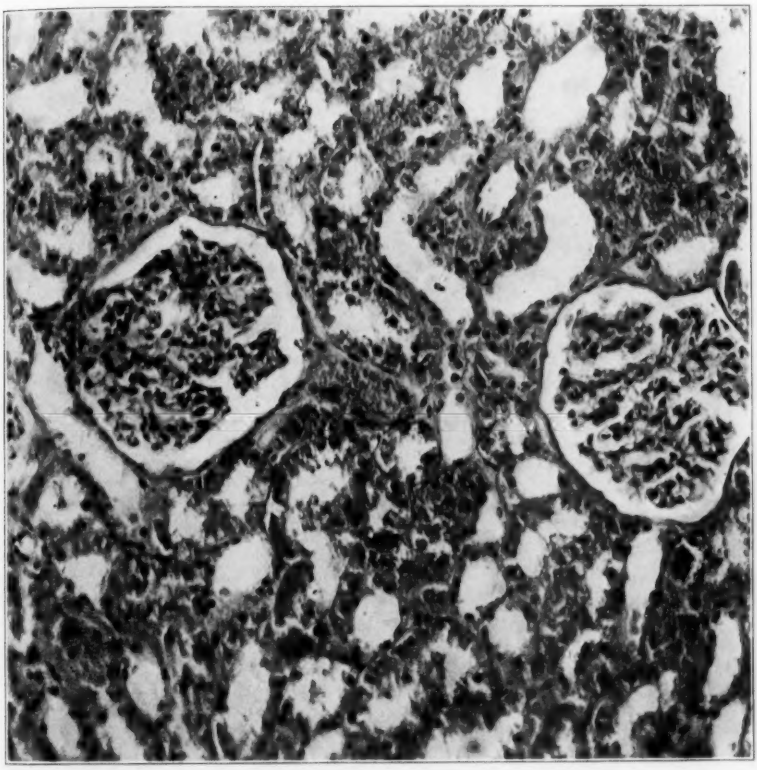

Fig. 2 (dog 6).—Microscopic section of kidney (× 270) before intravenous injection of 100 cc. of 50 per cent solution of sucrose.

granular. The urine of this animal showed 15 to 20 red blood cells per high power field in the daily sediment.

Dogs 14 and 5 were then subjected to daily doses of 100 cc. for eight and six days, respectively, and killed two days after the last injection. Comparison of the microscopic sections of the kidneys taken before injection and after death showed no marked changes for dog 14, although

the daily urinary sediment had revealed a 2 to 4 plus reaction for albumin, red blood cells and casts; dog 5 showed moderate hyperemia and signs of early degeneration, with hemorrhages and early necrosis of the tufts in the glomeruli. Throughout the cortex, the proximal and distal convoluted tubules and loops of Henle revealed cells with swollen and granular cytoplasm, which took a faint stain with eosin.

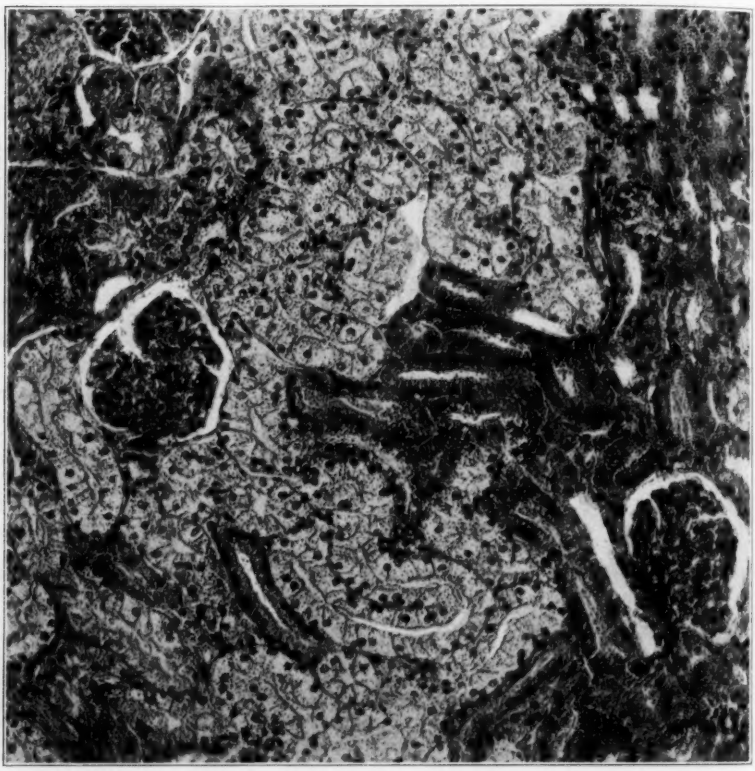

Fig. 3 (dog 6).—Microscopic section of kidney (× 210) twenty-four hours after intravenous injection of 100 cc. of 50 per cent solution of sucrose. The changes observed are those of marked hyperemia of the glomeruli and the tubules, as well as intense edema of the tubules draining the affected glomeruli, to the point of obliteration of the lumens in many cases. (Compare with figure 2.)

The tubules draining the damaged glomeruli were in various stages of degeneration.

Finally, it was decided to study the renal changes which might result from a single injection of the substance. For this purpose 4 dogs

(6, 9, 10 and 11) were first subjected to renal biopsy and after recovery were given a single dose of 100 cc. of 50 per cent sucrose. They were then killed after twenty-four, seventy-two, one hundred and twenty and one hundred and sixty-eight hours, respectively. Microscopic study of the kidneys at that time showed a rather clear course of events. After twenty-four hours the changes were those of hyperemia and marked

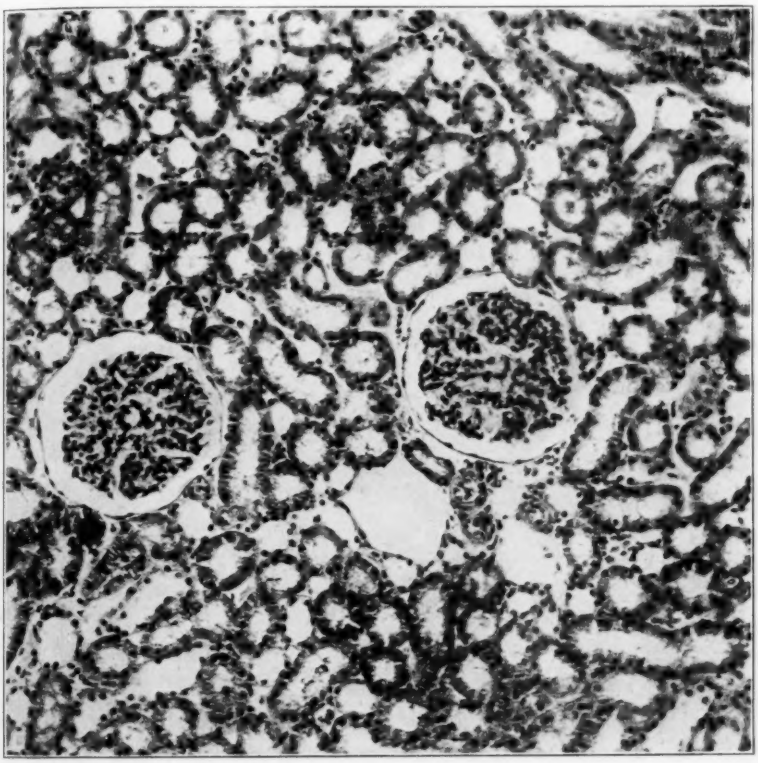

Fig. 4 (dog 9).—Microscopic section of kidney (× 210) before injection of 100 cc. of 50 per cent solution of sucrose.

edema of the tubules, almost to the point of obliteration of the lumens. After seventy-two hours the changes had reached the peak, as evidenced by fairly marked glomerular and interstitial hyperemia, with sloughing of the lining epithelium of the tubules, the cells of which contained pale swollen nuclei. The changes noted after one hundred and twenty hours were definitely less, and after one hundred and sixty-eight hours restitution had taken place. These findings are in essential agreement with

those of Helmholz. Figures 2 and 3 (dog 6), 4 and 5 (dog 9) and 6 and 7 (dog 10) show the microscopic changes observed.

ANIMAL EXPERIMENTS WITH D-SORBITOL

In the series of experiments with d-sorbitol, dogs (216 to 220) were subjected to preliminary biopsy of the kidney, and 100 cc. of 50 per cent

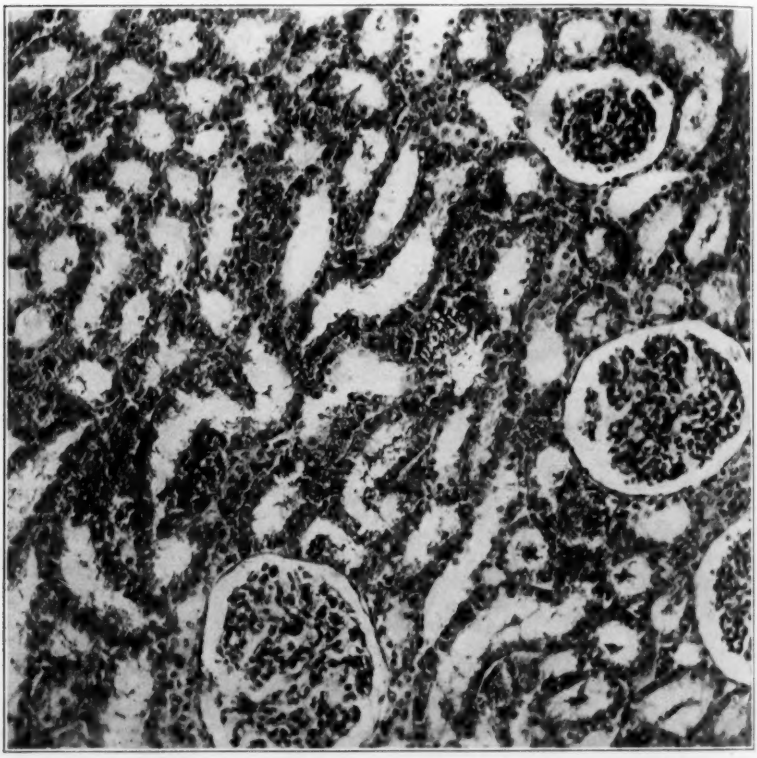

Fig. 5 (dog 9).—Microscopic section of kidney (× 210) seventy-two hours after injection of 100 cc. of 50 per cent solution of sucrose, showing moderate capillary congestion. The tubular epithelium shows cytolysis and sloughing of tubular epithelium, in some cases leaving only the basement membranes as an outline of the tubule. (Compare with figure 4.)

solution of d-sorbitol was injected. The dogs were killed twenty-four, forty-eight, sixty-nine, one hundred and twenty and ninety-six hours after injection, respectively. Comparison of sections of kidney removed

from these animals at the time of death with the biopsy specimens revealed no alterations. Two more dogs (221 and 222) were given 50 per cent solution of d-sorbitol intravenously in doses of 100 cc. daily for ten and nine consecutive days, respectively. The latter dog died fifteen hours after the last injection, and at autopsy an abscess was seen at the site of the original incision for biopsy. The former dog (221) was

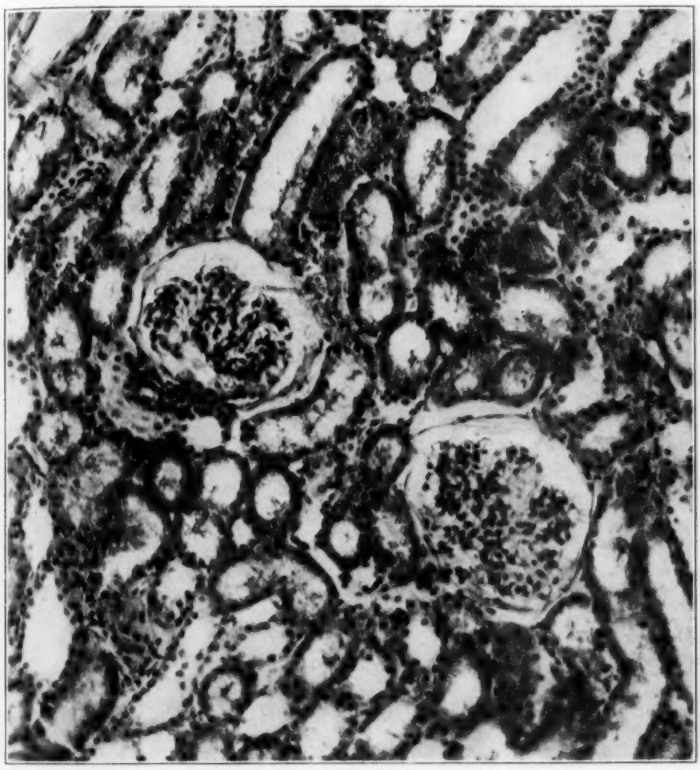

Fig. 6 (dog 10).—Microscopic section of kidney (× 210) before administration of 100 cc. of 50 per cent solution of sucrose.

killed twenty-four hours after the last injection. Neither of the dogs showed significant alterations in the kidneys at the time of death according to microscopic comparison of postmortem sections with biopsy specimens taken preliminary to the experimental period.

ANIMAL EXPERIMENTS WITH 50 PER CENT SOLUTION OF DEXTROSE

Since the action of sucrose on the dog's kidney was already known to us, it was felt that if the outlines of the experimental procedure used

in the study of the effects of that substance were followed with dextrose and with sodium chloride, ample data for comparison would be available without undue sacrifice of time and of animals. Accordingly, in each of the following series only 3 dogs were used. One dog of each series was given injections daily for ten days and killed forty-eight hours after the last injection. Two other dogs in each series were given single injec-

Fig. 7 (dog 10).—Microscopic section of kidney (× 210) one hundred and twenty hours after administration of 100 cc. of 50 per cent solution of sucrose, showing changes in tubules similar to those in figure 5. However, cells of the tubules show evidence of restitution. The glomeruli are definitely contracted, with evidences of early degeneration of glomerular epithelium. (Compare with figure 6.)

tions and killed twenty-four and seventy-two hours later. From our experience with the injection of sucrose we were satisfied that we could detect renal lesions if they occurred, whereas if they did not occur under

these experimental conditions we could feel equally safe in stating that the compounds we were injecting were innocuous. In addition, abundant pathologic material from patients to whom 50 per cent solution of dextrose or 10 per cent solution of sodium chloride had been administered before death attested to the harmless nature of these substances, at least in relation to the kidneys.

Dog 223 was given ten daily injections of 100 cc. of 50 per cent solution of dextrose intravenously and killed forty-eight hours after the last injection. Dogs 225 and 227 were each given a single injection of 100 cc. of 50 per cent solution of dextrose intravenously and killed twenty-four and seventy-two hours later, respectively. Comparison of the microscopic sections of the kidneys taken at the time of death with those obtained by biopsy before injection failed to reveal significant alterations, in contradistinction to the effects observed in the comparable series of experiments in which sucrose was used.

ANIMAL EXPERIMENTS WITH 10 PER CENT SOLUTION OF SODIUM CHLORIDE

In like manner dogs 224, 226 and 228 were given intravenous injections of 50 cc. of 10 per cent solution of sodium chloride. Dog 224 received ten daily injections and was killed forty-eight hours after the last injection, while dogs 226 and 228 were given single injections and killed twenty-seven and seventy-two hours later, respectively. Here, too, no alterations of the kidneys were noted when sections were compared with biopsy specimens taken from these dogs before injection.

COMMENT

It is obvious from this work that the intravenous administration of 50 per cent solution of sucrose to dogs in doses comparable to those used clinically may be expected to produce renal lesions. These lesions reach the peak of severity three to five days after injection and, if permitted, will subside entirely by about the seventh day. Embarrassment of renal function, if present at all, is not measurable by present clinical methods in either dog or man. Prolonged daily administration tended to produce variable but marked renal lesions, with a delay in ability to make restitution. It is easily conceivable, therefore, that repeated administration of sucrose at intervals of several days might, by the summation of insults to the kidney and by the delay in restitution of the previously injured tissue, eventually cause considerable functional impairment of the kidneys. There was slight evidence in 1 case (dog 1) that permanent changes may ensue after prolonged administration. This animal's kidney showed evidences of hyalinization of occasional glomeruli. It is felt that in spite of the marked tubular changes seen regeneration of these structures was complete.

A marked inconsistency was noted between the urinary findings and the degree of renal involvement revealed histologically. No predictions concerning one could be made on the basis of the other. It can be assumed that if changes comparable to those noted in the dog are present in the normal human being impairment of renal function in the latter may occur. Unfortunately, the tests were not extended over the entire week following the injections, so that evidence of impairment of function during the time when the renal lesion could be expected to be maximal was not obtained. On the other hand, even human subjects with impaired renal function showed no further functional embarrassment as a result of the injection.

CONCLUSIONS

1. A single dose of 200 cc. of 50 per cent solution of sucrose administered intravenously to normal human beings and to those with existing impairment of renal function produces no significant change in the results of renal function tests.

2. Anatomically, after a comparable clinical dose of sucrose injected into dogs, changes in the kidneys, by comparison of postmortem sections with the normal biopsy specimen taken in each case, were seen to be fairly marked.

3. The morphologic changes are transitory, reaching their height between the third and the fifth day after injection of sucrose, with a marked tendency to complete restitution. Only after prolonged repeated administration does there seem to be some evidence of permanent glomerular change. Prolonged administration tends in some cases to delay restitution.

4. Although the likelihood of impairment of renal function by the clinical application of 50 per cent solution of sucrose is slight, the fact that morphologic changes are produced should be borne in mind and its indiscriminate use avoided.

5. The results of our experiments with the intravenous administration of 50 per cent solution of d-sorbitol to dogs, controlled with renal biopsy before injection, indicate that no renal alterations occur even after prolonged (ten days) daily injections of these doses.

6. The essential procedures carried out in the foregoing experiments were repeated for two additional series of dogs, 50 per cent solution of dextrose being used in one and 10 per cent solution of sodium chloride in the other. No renal injury could be noted by comparison of the microscopic appearance of the kidneys after death with that of biopsy specimens from the same dog before injection.

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INFLUENCE OF THE LIVER ON SERUM PHOSPHATASE

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AND
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BROOKLYN

The variable values for serum phosphatase in cases of hepatic disease have never been satisfactorily explained. Experimental work by previous investigators has not led to results that would clarify the interpretation of the serum phosphatase level in clinical hepatic and biliary disorders. Both clinically and experimentally, serum phosphatase rises in cases of extrahepatic biliary obstruction. The variable results obtained clinically in cases of hepatic disease led us to investigate the influence of the liver on the serum phosphatase by attempting to correlate the underlying pathologic picture in the liver with the resultant value for serum phosphatase.

PROCEDURES AND RESULTS

All the experimental procedures were carried out under anesthesia induced by intravenous administration of pentobarbital sodium and under aseptic technic.

In experiment 1, 3 dogs were used, 2 male and 1 female, each weighing approximately 30 pounds (13.6 Kg.). They were observed for ten days to establish the normal values for total cholesterol, free cholesterol, phosphorus, urea nitrogen and phosphatase, the normal icterus index, the variations of the metabolites during different parts of the day and the effects of the diet. Then by a pararectal or subcostal incision the abdomen was opened, and a single hepatic duct in 2 of the dogs was doubly ligated. In the third dog, one of the major hepatic ducts and the cystic duct were doubly ligated. The dogs did well after the operation and made uneventful recoveries. Venous blood was drawn for the aforementioned determinations every forty-eight hours for eight days after the operation and afterward at greater intervals.

The results show that after obstruction in a part of the biliary system a significant rise in phosphatase, total cholesterol and percentage of free cholesterol occurred. The icterus index did not rise. All the values returned to normal after six to eight weeks.

Necropsy revealed that the hepatic lobes the ducts of which were ligated were markedly atrophied (fig. 1). The hepatic architecture of these lobes was indistinct.

From the Department of Laboratories, Divisions of Biochemistry and Pathology, Jewish Hospital of Brooklyn, Dr. Max Lederer, Director.

Fig. 1.—Atrophy of the lobes of the liver after ligation of a single duct.

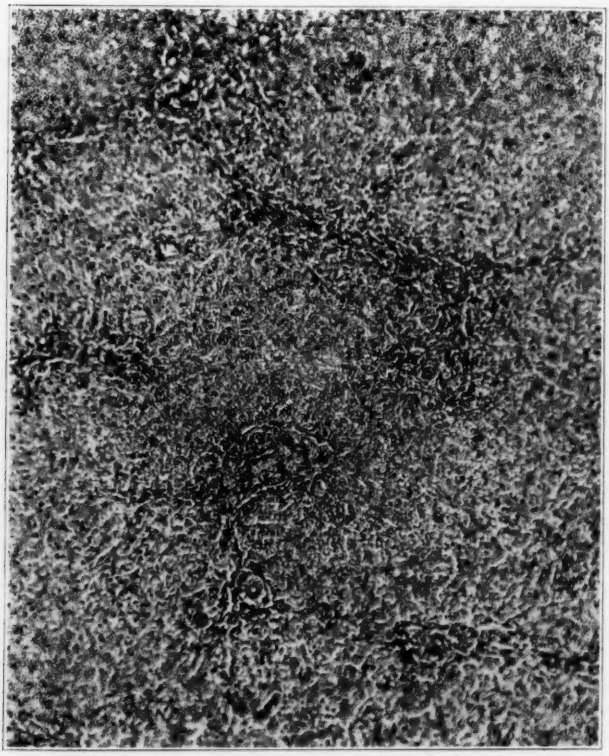

Fig. 2 (× 130).—Microscopic appearance of the atrophied lobe of the liver.

The microscopic picture was that of marked atrophy of the lobules of the liver and congestion (figs. 2 and 3). The lobules were small and surrounded by a relatively large amount of periportal connective tissue. When cords of liver cells could be recognized, they were narrow and separated by broad sinuses filled with blood, so that the width of the cords compared to that of the sinuses was in reverse proportion. The cytoplasm was either pale staining or vacuolated. Only the nuclei

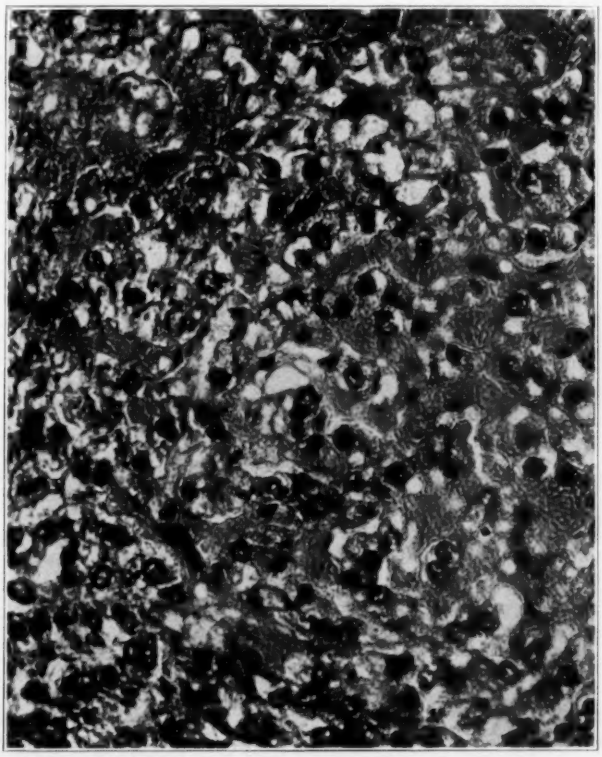

Fig. 3 (× 694).—High power magnification of the section shown in figure 2.

were rather well preserved. The lumens of the bile ducts were not widened. The latter showed no pathologic changes.

In experiment 2, 3 dogs were used. They were observed for several days, and the normal values for total cholesterol, free cholesterol, phosphorus, urea nitrogen and phosphatase and the normal icterus index were established. The common bile and the cystic duct of dog 4 (weight 25 pounds [11.3 Kg.]) were doubly ligated. The dog recovered satisfactorily from the operation. From two days after the operation on, 20 mg. of arsenic trioxide was injected intravenously daily.

A large necrotizing ulcer developed at the site of the operative incision. The dog died seven days after the operation.

The operative procedure was verified. Arsenic trioxide was found in the liver, kidney and skin.

After a complete biliary obstruction followed by intravenous injections of arsenic trioxide, the values for phosphatase rose to about ten times the normal value. There was a slight rise in the values for total cholesterol and in the percentage of free cholesterol.

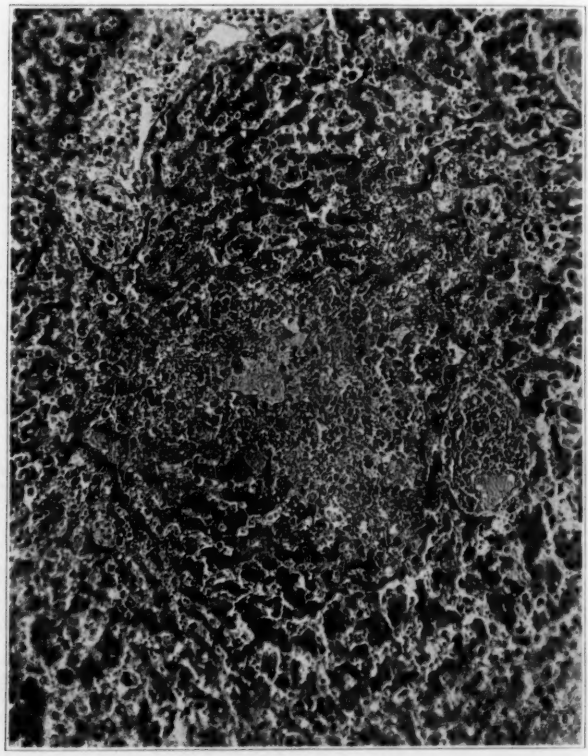

Fig. 4 (× 130).—Microscopic appearance of the liver after complete biliary obstruction and intravenous administration of arsenic trioxide.

In dog 5 (weight 30 pounds [13.6 Kg.]), after the control values were determined, 20 mg. of arsenic trioxide was injected intravenously daily for five days before the operation. The common bile and the cystic duct were doubly ligated—as in dog 4. Thirty-six hours after the ligation, the injections of arsenic trioxide were resumed. Forty-five milligrams of arsenic trioxide was injected in two days. The administration of arsenic was then discontinued. The dog recovered from the

operation. After thirteen and one half days, when the dog seemed to be recovering, injection of 80 mg. of arsenic trioxide in an attempt to produce severe damage was fatal in three hours.

The operative procedure was verified. Arsenic was found in the liver, skin and kidney.

The results of the procedures were similar to the results obtained on dog 4; namely, after complete biliary obstruction and intravenous administration of arsenic

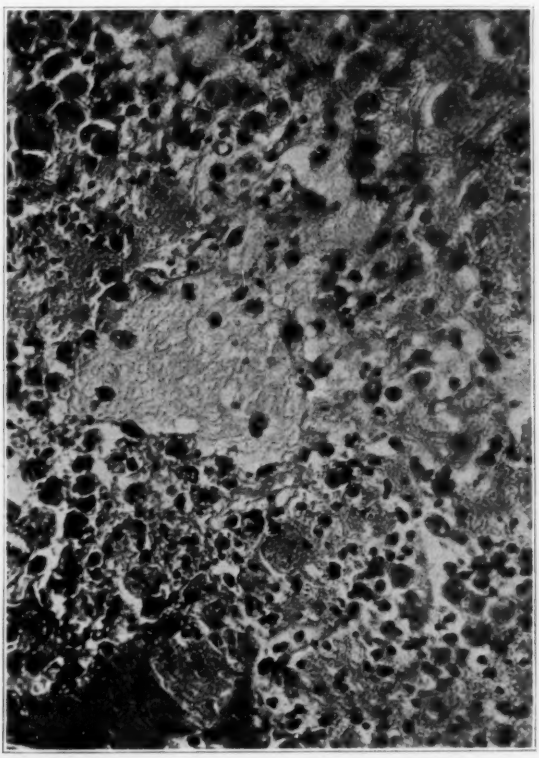

Fig. 5 (× 640).—High power magnification of the section shown in figure 4.

trioxide the serum phosphatase rose to about ten times the normal value. A similar result was found in the cholesterol values.

The microscopic appearance of the liver in this animal was that of central necrosis with hemorrhage. The cords of liver cells in the central part of the lobules were destroyed and replaced by amorphous pink-staining material. The cords toward the periphery of the liver lobules were separated by sinuses which were distended with blood. Areas of extravasated blood also were present. Many of the liver cells contained brown bile pigment. The periportal connective tissue

TABLE 1.—*Results of Ligation of a Single Hepatic Duct*

Time After Ligation, Days	Total Cholesterol	Free Cholesterol, %	Phosphorus	Phosphatase	Icterus Index
		Dog 1			
Before ligation	180	23	3	3.5	2.5
½	179	22	3.1	16.6	2.0
2½	227	23	3.4	51.6	3.9
4½	220	31	3.1	56.0	2.5
7½	288	23	4.2	45.8	2.5
13½	396	25	4.9	40.4	3.3
18	312	21	5.0	29.4	2.0
23	248	20	...	13.0	2.0
30	276	21	4.2	6.8	2.2
39	227	21	2.6	3.8	2.0
		Dog 2			
Before ligation	225	22	3.6	3.2	2.0
1	324	..	4.7	15.0	2.5
4	318	45	4.6	39.4	3.6
7	269	47	2.7	50.8	...
10	327	31	4.6	47.0	...
16	257	26	4.4	41.1	...
40	254	20	5.5	18.0	2.5
55	...	..	3.7	3.7	2.0
		Dog 3			
Before ligation	168	25	4.1	1.8	2.8
1	207	30	3.0	15.5	3.0
3	239	..	3.6	28.4	7.5
18	341	43	3.3	39.7	2.5
30	379	28	3.5	72.5	3.0
39	231	25	...	40.7	2.5
50	216	22	3.5	17.0	3.5
58	199	25	3.9	10.2	...

TABLE 2 (dog 4).—*Results of Ligation of the Common Bile and the Cystic Duct with Subsequent Administration of Arsenic*

Time After Ligation, Days	Total Cholesterol	Free Cholesterol, %	Phosphorus	Phosphatase	Icterus Index
Before ligation	170	26	3.6	5.2	2.5
1	260	35	5.8	46.0	23.0
	(Administration of Arsenic Started)				
3	278	22	4.1	43.4	23.0
4	275	32	5.3	47.2	33.0
5	280	26	6.3	46.2	30.0
6	230	31	8.0	44.5	31.0

TABLE 3 (dog 5).—*Results of Ligation of the Common Bile and the Cystic Duct with Preparatory and Subsequent Administration of Arsenic*

Time After Ligation, Days	Total Cholesterol	Free Cholesterol, %	Phosphorus	Phosphatase	Urea Nitrogen	Icterus Index
Before medication	213	38	5.0	2.7	22.2	..
	(Administration of Arsenic Started)					
Before ligation	187	26.2	4.4	1.1	13.5	..
14 hr.	250	43.2	5.0	36.0	11.0	58
1½	256	35.7	4.9	45.5	8.0	60
	(Administration of Arsenic Resumed)					
3½	258	33.7	5.4	51.4	10.0	40
5½	306	36.0	3.6	48.9	7.5	55
8½	312	44.0	5.4	40.6	9.0	39
11½	266	37.0	4.2	49.0	6.5	33

was infiltrated with large mononuclear cells and a few polymorphonuclear leukocytes (figs. 4 and 5).

In dog 6 of experiment 2 a similar obstruction was created. The dog made an uneventful recovery from the operation.

After complete biliary obstruction the serum phosphatase rose about forty-fold. The total cholesterol rose markedly and the percentage of free cholesterol moderately.

As a control, the abdomens of 2 dogs were opened, and the gallbladder and liver were manually and instrumentally handled. During the following fourteen days no changes in serum phosphatase were noted.

COMMENT

In the first experiment, the obstruction of only a small part of the biliary system produced a marked rise in serum phosphatase. Not

TABLE 4 (dog 6).—*Results of Ligation of the Cystic and the Common Bile Duct Without Medication*

Time After Ligation, Days	Total Cholesterol	Free Cholesterol, %	Phosphorus	Phosphatase	Urea Nitrogen	Icterus Index
Before ligation...	215	27	3.9	3.9	22.0	....
½.....	321	..	3.8	31.8	20.0	24.8
2½.....	308	38	4.5	57.5	20.0	39.0
5½.....	335	54	...	72.0	14.0	47.0
9.....	289	35	4.2	112.0	18.0	51.0
11.....	400	..	4.8	140.0	16.4	....
16.....	478	..	5.6	200.0	15.0	....

enough obstruction was produced to cause an accumulation of bile pigments (jaundice), since it has been proved experimentally that if one seventh of the biliary system in dogs remains open, jaundice does not occur.[1] Apparently, the metabolic functions of the liver were not seriously interfered with, except for the temporary rise in total cholesterol and in the proportion of free cholesterol. This phase of the work has been fully investigated clinically by Epstein and Greenspan[2] and experimentally by Hawkins and Wright.[3] According to the values recorded by the latter investigators, the results which we obtained were still within normal limits. However, the methods of determination which we used for cholesterol and ester concentrations differed from

1. Markowitz, J.: Textbook of Experimental Surgery, Baltimore, William Wood & Company, 1937.

2. Epstein, E. Z., and Greenspan, E. B.: Clinical Significance of the Cholesterol Partition of the Blood Plasma in Hepatic and Biliary Diseases, Arch. Int. Med. **58**:860 (Nov.) 1936.

3. Hawkins, W. B., and Wright, A.: J. Exper. Med. **59**:427, 1934.

those employed by the investigators mentioned. The values which we obtained were definite elevations as compared with those recorded for a series of 12 control dogs kept under observation for two weeks.

Figure 6 illustrates the typical rise in phosphatase when partial biliary obstruction is produced. After six to eight weeks the values return to normal limits. If one were to determine the value for serum phosphatase after fifty days of obstruction there would be no way of telling that an obstruction had ever existed. Therefore, serum phosphatase may be normal in the presence of a partial extrahepatic obstruction.

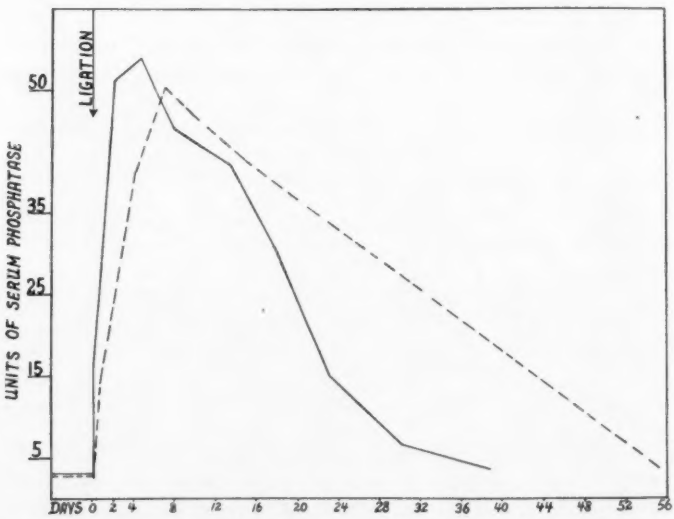

Fig. 6.—Changes in serum phosphatase after ligation of a single duct. The solid line represents observations on dog 1; the broken line, those on dog 2.

The cause of the steady decrease in the values for serum phosphatase in the presence of a permanent obstruction and of the occurrence of normal phosphatase when an extrahepatic obstruction is present may help to explain the variable results obtained in cases of hepatocellular disease. We believe that the results obtained were due to the lack of properly functioning liver cells secreting their products into the biliary channels which were obstructed. Therefore, in spite of the extrahepatic obstruction, still present after six to eight weeks, the phosphatase values were within normal limits. The gross and microscopic appearance of this portion of the liver indicated that the obstruction was still present

but the corresponding portion of the liver had atrophied. In dog 3 in the first experiment, the same phenomenon occurred, but it took a longer time.

Experiment 2 confirmed the opinion that in addition to an extrahepatic obstruction, there must be a good physiologic state of the liver cells for a rise in serum phosphatase to occur. When the liver cell was not damaged, an obstruction of the common bile duct caused a rise in serum phosphatase to more than twice the value that appeared with a

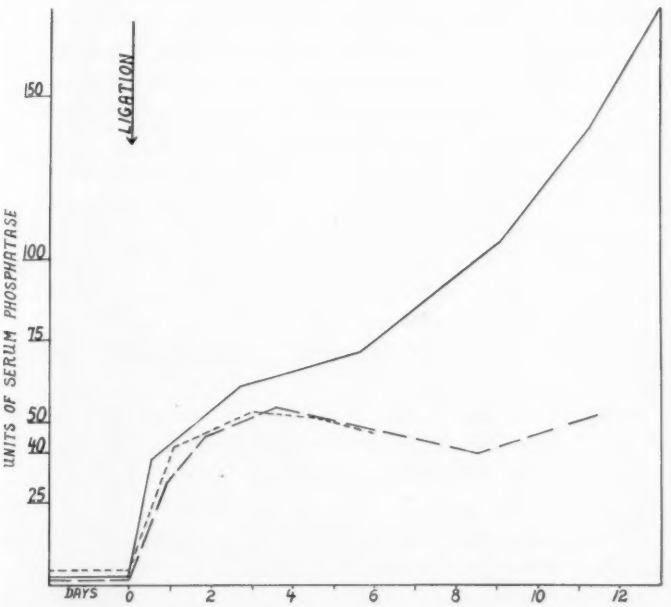

Fig. 7.—Comparison of results of complete biliary obstruction and intravenous administration of arsenic trioxide in dogs 4 and 5 and complete biliary obstruction in dog 6. The solid line represents observations on dog 6; the line of long dashes, those on dog 5, and the line of short dashes, those on dog 4.

similar obstruction when the liver cells were additionally damaged by arsenic trioxide. The cholesterol rose to higher levels in the case of obstruction without damage to the liver cells. Once again, our results were in accordance with Epstein and Greenspan's observations. Microscopic examination bore out the fact that in dogs 4 and 5, to which arsenic trioxide was given, the parenchyma of the liver was damaged.

Clinical and experimental evidence indicates that the liver cells play no part in the formation of bile pigment except that of secreting it into the bile ducts. This is not the case for phosphatase metabolism, and probably explains the difference in values in the hepatocellular type of jaundice.

Thannhauser and his co-workers [4] postulated that the increase in the amount of serum phosphatase in disease is not an actual increase in enzyme but merely an activation of enzyme normally present. The increased activity in jaundice is dependent on an activating substance (a cofactor, or coenzyme, which has not yet been determined) and a depressing substance (like bile salts). With obstruction, they concluded, there is a damming up of both, but since the cofactor is more powerful as an activating agent than bile acids are as depressors, the net result is an increase in activity of serum phosphatase.

It is difficult to place the knowledge of a cofactor and depressant substance in the picture shown by our experiments. Granted that there was a damming up of both substances in the case of extrahepatic obstruction, it seems likely that both substances would also accumulate in hepatocellular disease, in which some degree of obstruction usually exists. To theorize in this connection offers several interesting possibilities:

1. The coenzyme or activating principle may be destroyed when the liver cell is damaged.

2. In cases of damage to the liver cell there may be much greater production of the depressant substance, as for example the bile salts. This may account for the greater percentage of free cholesterol found in cases of this variety.

3. Perhaps a depressant substance which is so powerful in its action may pass from the small intestines, be brought to the liver and there be acted on in one of two ways, as the bile pigments are acted on by the liver. In cases of intrahepatic jaundice, this depressant substance may pass to the liver without being affected by the liver cells and therefore accumulate in the blood stream. In cases of obstructive jaundice, this substance is brought into the liver cell and is there acted on and consequently loses its depressant activity. This second process may resemble the change that the liver cell produces on bile pigments to make it diffusible and give the direct van den Bergh reaction.

The most likely explanation is that the production of an activating substance by the liver is diminished when the liver cell is damaged.

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4. Thannhauser, S. J.; Reichel, M.; Grattan, J. F., and Maddock, S. J.: J. Biol. Chem. **121**:715, 1937.

SUMMARY

1. Serum phosphatase values increase more than tenfold after ligation of a single hepatic duct. No other important changes in the blood result from this procedure.

2. After the rise that follows obstruction of a single hepatic duct, the values steadily decrease and in thirty to fifty-five days return to normal limits.

3. Obstruction of the common bile duct in a dog causes a rise in serum phosphatase more than twice that which follows a similar obstruction in other dogs whose livers have been damaged by intravenous administration of arsenic trioxide.

CONCLUSION

The resultant values of serum phosphatase in hepatic and biliary disorders are dependent on two equally important factors: (*a*) the degree and extent of biliary obstruction and (*b*) the functional state of the liver cell.

VITAMIN C AND THE AGING EYE

AN EXPERIMENTAL CLINICAL STUDY

S. MILES BOUTON Jr., M.D.
DETROIT

In the course of routine refraction tests on a number of patients at the Hastings State Hospital during the late summer months of 1937, clouding of the optic media associated with more or less impaired vision was noted in an undetermined percentage of cases; apparently this was a precursor of senile cataract, a concomitant feature of early cataract or a morbid condition per se. The patients ranged in age from 41 to 73 years, represented both sexes and included workers and nonworkers. None was a newcomer to the institution. Only a small percentage of this group could be classed as actually senile. In view of references in the literature within the past few years to changes in the vitamin C content of the lens and of other structures of the eye in cataractous conditions (to be discussed later in this paper) and in view also of the combination of circumstances which conceivably might lead to vitamin C deficiency at this institution (geographic location, nature of diet and other factors), it was thought that an investigation into the status of the hospital population in this regard might prove enlightening.

Such an investigation seemed further indicated by the rather frequent occurrence of minor infections of the upper respiratory passages among the patients at this institution during the winter months, the occasionally extremely poor progress in the healing of decubitus ulcers and other lesions involving loss of skin, despite apparently insufficient clinical grounds for such delay, and the observation that some of these decubitus ulcers improved promptly and markedly after the administration of large quantities of tomato juice.

Attention is called to the work of Wolbach,[1] von Jeney and Törö[2] and Lanman and Ingalls[3] concerning the role of vitamin C in the forma-

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From the Hastings State Hospital, Ingleside, Neb.; Juul C. Nielsen, M.D., Superintendent.

1. Wolbach, S. B.: Controlled Formation of Collagen and Reticulum: A Study of the Source of Intercellular Substance in Recovery from Experimental Scorbutus, Am. J. Path. (supp.) **9**:689, 1933; Vitamin C and the Formation of Intercellular Material, New England J. Med. **215**:1158 (Dec. 17) 1936; The Pathologic Changes Resulting from Vitamin Deficiency, J. A. M. A. **108**:7 (Jan. 2) 1937.

(Footnotes continued on next page)

tion of intercellular material and thus in repair of wounds, and to the observations of Perla and Marmorston,[4] Jusatz,[5] Hetler,[6] Cady,[7] McCullough[8] and Takahashi[9] on the role of vitamin C in the maintenance of resistance to infection and in the prevention of disturbances of the respiratory passages in cases of scurvy.

In the optic media of the eye, which represent various types of tissue, any change in character, specifically any impairment of metabolism and nutrition, is readily manifested in decreased transparency and thus in measurable impairment of vision. It would seem logical, therefore, to search for a correlation between the degree of vitamin C saturation of the body and the presence of visual disturbances. The work here reported represents an attempt to determine the relation between the blood level of vitamin C, its excretion in the urine and the condition of the optic media, as well as the reaction of the latter to treatment with this substance.

No general review of the literature on vitamin C will be attempted in this report, but attention is called to the various comprehensive reviews at present available.[10]

The minimum daily intake of ascorbic acid required by a normal adult in order to maintain an adequate blood level is, according to

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2. von Jeney, A., and Törö, E.: Die Wirkung der Ascorbinsäure auf die Faserbildung in Fibroblastkulturen, Virchows Arch. f. path. Anat. **298**:87, 1936; abstracted, Arch. Path. **24**:670 (Nov.) 1937.

3. Lanman, T. H., and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing, Ann. Surg. **105**:616 (April) 1937.

4. Perla, D., and Marmorston, J.: Role of Vitamin C in Resistance, Arch. Path. **23**:543 (April); 683 (May) 1937.

5. Cevitamic Acid Stimulation of Specific Antibody Production, editorial, J. A. M. A. **109**:714 (Aug. 28) 1937.

6. Hetler, R. A.: Nutrition and Infections of Respiratory Mucous Membranes, Ann. Otol., Rhin. & Laryng. **46**:629 (Sept.) 1937.

7. Cady, F. C.: Association of Scurvy with Oral Diseases, Pub. Health Rep. **52**:1526 (Oct. 29) 1937.

8. McCullough, N. B.: Vitamin C and Resistance of the Guinea Pig to Infection with Bacterium Necrophorum, Arch. Path. **25**:139 (Jan.) 1938.

9. Takahashi, cited by Wachsmuth, W., and Heinrich, G.: Hypovitaminose und Osteomyelitis, Klin. Wchnschr. **17**:269 (Feb. 19) 1938; abstracted, J. A. M. A. **110**:1529 (April 30) 1938.

10. (*a*) Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **61**:297 (Feb.) 1938. (*b*) Booth, M., and Hansen, A. E.: The Present Day Status of the Vitamins: A Review, Journal-Lancet **57**:530 (Dec.) 1937. (*c*) Wright, I. S., and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), with Especial Reference to Its Effects on Capillary Fragility, Arch. Int. Med. **57**:241 (Feb.) 1936. (*d*) Perla and Marmorston.[4]

Göthlin [11] and Abbasy and his co-workers,[12] about 25 mg. Schultzer's [13] recent work confirmed this. Apparently no symptoms are known to be associated with excessive intake. Determinations of the ascorbic acid level of the blood by various investigators have given roughly comparable results, so that it is possible at present to determine at least approximately what may be considered a normal level and what a minimum level, below which one may presume a deficient intake. According to Mirsky, Swadesh and Soskin,[14] the total ascorbic acid content of whole blood ranges between 1.11 and 2.88 mg. per hundred cubic centimeters. Farmer and Abt [15] found values of from 0.69 to 2.36 mg. per hundred cubic centimeters for reduced ascorbic acid content of blood plasma. Bellows,[16] in a comparison of the ascorbic acid levels in the blood plasma of normal and of cataractous persons, found average values of 1.02 and 0.605 mg. per hundred cubic centimeters, respectively. In another report by Farmer and Abt,[17] these authors stated that an ascorbic acid content of the blood plasma reduced to less than 0.50 mg. indicates "marked insufficiency of vitamin C intake," while Ingalls and Warren [18] stated that they considered levels below 0.30 mg. indicative of asymptomatic scurvy. Later references to the level of this substance in the blood [19] specified 0.70 mg. per hundred cubic centimeters as an

11. Göthlin, G. F.: Method of Establishing a Vitamin C Standard and the Requirements of Physically Healthy Individuals by Testing the Strength of the Cutaneous Capillaries, Skandinav. Arch. f. Physiol. **61**:225 (May) 1931; cited in Human Requirement for Vitamin C, editorial, J. A. M. A. **110**:1928 (June 4) 1938.

12. Abbasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, Lancet **2**:1399 (Dec. 21) 1935.

13. Schultzer, P.: On Saturation of Scurvy Patient with Small Doses of Ascorbic Acid: Consideration of Daily Human Requirement, Biochem. J. **31**: 1934 (Nov.) 1937.

14. Mirsky, Swadesh and Soskin, cited by Stephens, D. J., and Hawley, E. E.: The Partition of Reduced Ascorbic Acid in Blood, J. Biol. Chem. **115**:653 (Oct.) 1936.

15. Farmer, C. J., and Abt, A. F., cited by Stephens, D. J., and Hawley, E. E.: The Partition of Reduced Ascorbic Acid in the Blood, J. Biol. Chem. **115**:653 (Oct.) 1936.

16. Bellows, J.: Biochemistry of the Lens: V. Cevitamic Acid Content of the Blood and Urine of Subjects with Senile Cataract, Arch. Ophth. **15**:78 (Jan.) 1936.

17. Farmer, C. J., and Abt, A. F.: Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med. **34**:146 (March) 1936.

18. Ingalls, T. H., and Warren, M.: Frequency of Asymptomatic Scurvy in Patients on Bland Diets, New England J. Med. **217**:443 (Sept. 9) 1937.

19. Perla and Marmorston.[4] Wilder and Wilbur.[10a]

approximate (or minimum) average [20] value in normally nourished persons.

Among reports in the literature on values for urinary excretion, it will suffice to refer to Youmans and his associates,[21] who stated that "a daily urinary excretion of . . . 20 mg. . . . is suggested as the lower limit of normal daily excretion," and to Abbasy and his co-workers,[12] who asserted that "about 20 mg." is the average daily excretion of a normal adult receiving an adequate diet in England and stated that 10 to 15 mg. should be considered a minimum level, below which a substandard diet may be presumed.

In view of the fact, however, that ascorbic acid is excreted in some amount in the urine of every person not actualiy bedfast with scurvy, determinations of the presence of this substance in single specimens of urine occasionally give a far from adequate picture of the actual state of deprivation. The administration of accurately measured test doses, either intravenously or by mouth, with subsequent determination of the amount of the vitamin excreted during a measured period, has therefore been introduced as of value in establishing a diagnosis of subclinical scurvy and vitamin subnutrition of all degrees. The dose given perorally differs according to different investigators, ranging from 200 to 600 mg. or more. Abbasy and his co-workers [12] stated that the diet may be presumed to be "unduly low in vitamin C content" if there is no response to a single test dose of 700 mg. on the second day after administration. Youmans and his associates [21] stated that "for the present" excretion of 30 per cent of a test dose of about 600 mg. by adults may be taken to indicate the lower limit of "saturation."

In the field of ophthalmology, the most fruitful work is that dealing with the general role of the vitamins in the normal and abnormal metabolism of the eye,[22] as there appears to exist a close interrelation between the effects of several vitamins, notably A, C and G (riboflavin), on the oxidation-reduction processes of the various structures of the eye. Buschke [22a] pointed out that the crystalline lens, because of its eminent suitability for research of this kind, was one of the first organs in which the water-soluble oxidation-reduction systems, vitamins C and G, glutathione and the "oxidation catalyzer," vitamin A, could be demonstrated as coexistent. A considerable amount of work has been done in connection with the presence of vitamin C in the anterior chamber

20. Wortis, H.; Wortis, S. B., and Marsh, F. I.: Rôle of Vitamin C in Metabolism of Nerve Tissue, Arch. Neurol. & Psychiat. **39**:1055 (May) 1938.

21. Youmans, J. B.; Corlette, M. B.; Akeroyd, J. H., and Frank, H.: Studies of Vitamin C Excretion and Saturation, Am. J. M. Sc. **191**:319 (March) 1936.

22. (*a*) Buschke, W.: Die Vitamine in der Ophthalmologie, Ztschr. f. Vitaminforsch. **5**:37 (Jan.) 1936. (*b*) Pavía, J. L., and Diez, M.: Las vitaminas A y C en oftalmologia, Rev. oto-neuro-oftal. **12**:13 (Jan.) 1937.

and in the lens with normal and with pathologic conditions. Of special interest in connection with the work here reported are repeated determinations of the concentration of the vitamin in eyes with cataractous conditions and with aphakia,[22] all results pointing to a definite reduction of the vitamin with these conditions, especially the latter, and in the amount of the reduction in the presence of cataract more or less corresponding with the degree of opacity of the lens.

Reports on attempts to apply this information clinically, however, are difficult to find. One reference to such work among American clinicians is that of treatment with vitamin C and a diet rich in glutathione of a group of patients suffering from cataracts caused by dinitrophenol,[23] in which "rapid improvement" was noted. One report from England [24] described the "very favorable reaction" of a patient with congenital cataract to administration of vitamins A and C, as measured both by reading tests and by ophthalmoscopic examination.

Since ascorbic acid therapy was begun at this institution, reprints were received of work performed in Buenos Aires, by Pavía,[25] on cataractous persons of advanced age. Ascorbic acid was administered both intravenously and directly into the anterior chamber of the eye, and the effects were checked by biomicrographic study of the lens. Despite the fact that some of the patients treated had suffered impairment of vision for a number of years, the percentage of improvement was gratifying (70 per cent in 10 cases). The results were much poorer in a series of 7 patients treated with subcutaneous injections only. The amounts of ascorbic acid administered in the latter instance were, however, not especially large. Of special interest is the finding that the improvement in the condition of the optic media and consequently in the visual acuity of 1 patient persisted during two months of observation after institution of treatment, despite a gradual drop of the urinary excretion values of ascorbic acid. The author concluded that this phenomenon tends to bear out other investigative work which indicates that the ascorbic acid content of the anterior chamber can remain high regardless of the level in the blood plasma.

Pavía determined the amount of ascorbic acid to be administered by titrating the amount excreted in the urine; he came to the conclusion that when this figure goes below 3 mg. per hundred cubic centimeters with excretion of a normal twenty-four hour volume of urine, it is necessary to administer 300 mg. of ascorbic acid daily and that when the

23. Josephson, E. M.: Ascorbic (Cevitamic) Acid in Cataract with Special Reference to Dinitrophenol Cataracts, Science **82**:222 (Sept. 6) 1935.

24. Koepcke, G. M.: Vitamins and Infections of Eye, Nose, Throat and Sinuses, Journal-Lancet **57**:460 (Oct.) 1937.

25. Pavía, J. L.: Catarata senil: Un nuevo tratamiento medico, Rev. oto-neuro-oftal. **12**:182 (July) 1937.

content exceeds 3 mg., it is necessary to give only 100 mg. every other day. In Pavía's cases the duration of treatment was apparently determined entirely by the degree of improvement obtained. The author, however, did not specify the length of treatment he considered adequate definitely to determine whether any beneficial effect is to be expected.

Other references to dosage include a statement by Ingalls [26] to the effect that Johnson and Zilva and Hawley and his associates noted "no significant increase" in the excretion of ascorbic acid by unsaturated persons after daily administration of 200 mg. for several days. He also cited van Eekelen, who required 1,800 mg. for resaturation after abstaining for one month from foods containing vitamin C. There is, however, no reference to the manner in which this amount was taken nor to the time required. Youmans and others [21] stated that a daily dose of 25 to 100 mg., has little effect on the excretion value of unsaturated persons, and Wood [26a] described a patient who had frank scurvy with no ascorbic acid in the urine, who excreted 1 to 7 mg. after taking a dose of 600 mg. but none after that, despite a daily dose of 80 mg. for one week, with clinical improvement.

EXPERIMENTAL STUDY

In regard to the procedure to be followed at this institution, it seemed desirable to complete all tests within one season, in view of the fact that seasonal variations in the degree of ascorbic acid saturation may be assumed with a fair degree of certainty.[27]

It was decided to establish as many fairly large groups of approximate values as possible before investigation of the special group of patients who presented visual disturbances. Tests on the vitamin C level in the blood were carried out also on a small group of subjects not connected with this institution but living under similar conditions. They represent a part of the nursing staff of the general hospital at Hastings, Neb. Tests on this group were performed in April and May 1938.

It proved preferable, in the interests of cooperation and because of the fact that we were dealing with patients with mental disease, to run tests on several persons simultaneously for short periods, rather than long individual tests in the determinations of urinary excretion of the vitamin. No subject was tested without a preliminary complete analysis of urine, and all persons with definitely pathologic findings were rejected. Other requisites for inclusion in the test were subjective well-being, freedom, as far as determinable, from syphilis and active tuberculosis and absence of special treatment, such as metrazol or insulin shocks or therapy with the hypertherm.

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26. Ingalls, T. H.: Studies on the Urinary Excretion and Blood Concentrations of Ascorbic Acid in Infantile Scurvy, J. Pediat. **10**:577 (May) 1937.

26a. Wood, P.: A Case of Adult Scurvy, Lancet **2**:1405 (Dec. 21) 1935.

27. Corlette, M.; Youmans, J. B.; Akeroyd, J., and Frank, H.: A Clinical Study of Vitamin C Excretion, South. M. J. **29**:37 (Jan.) 1937.

Participants in the tests included the members of the medical staff and their wives, the members of the nursing staff, the day and the night attendants, confined patients and patients on parole as well as various employees of other types. All of these subjects ate all meals at the institution. As far as possible, men and women were chosen in equal numbers, with the exception of the outside group, which consisted entirely of women. The tests were begun in January 1938 and continued without interruption throughout February, March, April and May. All tests on the vitamin level in the blood and in the urine preparatory to controlled administration of ascorbic acid were completed by the end of March, i. e., at a time when the values would presumably be lowest.

The urine was collected in dark brown bottles; it was acidified to contain approximately 5 per cent glacial acetic acid and was kept at or near ice box temperature. Titrations were carried out at 8 a. m., 3 p. m. and 8 p. m. The urine was examined by titration of duplicate samples with 2,6-dichlorobenzenone-indophenol; the blood plasma was tested by the method of Farmer and Abt.[17] Blood was obtained by venipuncture, as a duplicate test, and occasionally other tests were made on each sample.

The first step in this series was a test on the twenty-four hour urinary excretion, carried out without any preparatory procedures and involving the largest number of subjects examined in any group. Some time later, twenty-four hour collections of urine were again undertaken, after the ingestion of .600 mg. of pure ascorbic acid in tablet form. The test dose was taken with breakfast, and collection of urine was started immediately; fresh fruits and fruit juices were eliminated from the diet during the period of collection, with no other change in the daily routine. In addition, the level of ascorbic acid in the blood plasma was determined, specimens of blood being taken in the morning during fasting.

The patients suspected of visual disturbances due to clouding of the media were first segregated by preliminary examination; they were then examined and grouped by a consulting ophthalmologist and were finally subjected to the tests on vitamin excretion and level in the blood just described. Before administration of ascorbic acid was begun as treatment, the series was narrowed to 12 patients, 8 women and 4 men. This number obviously represented only a fraction of the group of patients in whom difficulties of the same sort were encountered in refraction tests and in other tests at this institution. It was necessary, however, to pick subjects who could be counted on to describe their subjective impressions more or less accurately and consistently and whose mental conditions were not likely to change in the course of this investigation.

Homogeneity in every respect is not claimed for this group. All 12 persons, however, had in common subjective visual difficulties, especially in performing skilled tasks or in reading, and refraction could not be satisfactorily determined. If glasses were satisfactory when first fitted, they soon ceased to give good service. Three of the subjects, women 56, 64 and 73 years old, respectively, had well developed unilateral cataracts. One other, a woman aged 63, showed bilateral opacities of the lens; another woman, aged 47, had beginning bilateral cataracts.

For four weeks only 6 of the 12 subjects, 4 women and 2 men, received ascorbic acid. The remaining 6 served as controls in order that changes in the levels in the blood might be evaluated more accurately, as the oncoming change in seasons and the consequent change in the general diet were expected to bring about a general rise in the ascorbic acid reserves of the institutional population as a whole. Determinations of the vitamin level in the blood were carried out once a week on the subjects under treatment, except on the first subgroup for the fourth week, and on both subgroups after the fourth week. From the fourth week on, both

subgroups received ascorbic acid daily in addition to the regular diet. Small amounts of tomato juice were included as a regular fortifying feature of the diet five weeks after treatment was first begun (after one week for the second subgroup).

Treatment was begun with the administration of between 300 and 350 mg. of ascorbic acid daily. This dose was reduced for short periods in some cases, depending on the level in the blood, but at the conclusion of treatment (eight weeks for the first subgroup, four weeks for the second) 11 of the 12 subjects were receiving approximately 350 mg. daily. One patient did not receive any ascorbic acid during the last week of treatment. Determinations of levels in his blood plasma made during this week and those made subsequently are considered separately.

RESULTS

In a consideration of the findings, attention is first called to the difference in the average urinary excretion of ascorbic acid among the three large institutional groups. Only the values for the "officer" group (physicians and their wives, heads of the nursing departments, etc.) actually exceeded the minimum figures considered as indicative of

TABLE 1.—*Average Twenty-Four Hour Urinary Excretion of Ascorbic Acid* *

Subjects	Men and Women	Men	Women
25 officers	32.22	31.13	33.32
96 employees	14.96	16.65	14.03
Day workers	15.41	.....	.....
Night workers	13.70	.....	.....
31 patients†	10.94	10.64	11.22

* Values indicate milligrams.
† Excluding those treated with ascorbic acid.

normal vitamin C nutrition, while the values for the employee group (night and day attendants, clerical employees, etc.) hovered in the main around the minimum values cited in the literature, and the excretion levels of the patient group were, with only two or three exceptions, well below these values. The exceptions in the latter group, moreover, in no case exceeded the minimum normal values (table 1).

The levels in the blood plasma represented a parallel to the findings just cited—on the whole, however, with less marked differences between the three institutional groups (table 2).

The outside group of graduate and student nurses showed levels in the blood plasma closely approximating the averages given by Bellows and others, both in March and in May, with a slightly higher average in the later determinations (table 2).

The most striking and illuminating differences were obtained in determinations of excretion after a test dose (table 3). The practically complete failure on the part of the patients to eliminate any of the test dose within twenty-four hours is the outstanding finding for these sub-

jects. One woman, who lived in the same ward as other patients included in these tabulations, reflected the fact that she was receiving a high vitamin diet in the values for vitamin C after the test dose as well as, to a less complete degree, in the level in the blood plasma, but not at all in the regular urinary excretion of ascorbic acid. The latter was 11.58 mg. in twenty-four hours (highest value for a female patient taking the regular diet, 17.02 mg.; average for both sexes, 10.94 mg.). The level in the blood plasma was 1.00 mg. per hundred cubic centimeters (highest value for a female patient taking the regular diet, 0.50 mg.; average for both sexes, 0.49 mg.). The excretion of this

TABLE 2.—*Level of Ascorbic Acid* in Blood Plasma*

Subjects	Men and Women, Average	Men, Average	Women, Average	Highest Value
13 employees	1.12	0.97	1.24	1.90
16 patients†	0.49	0.51	0.47	0.65
15 members of outside group, March 9, 1938	0.70	....	....	1.20
6 members of outside group, May 24, 1938	0.76	....	....	1.30

* Values indicate milligrams per hundred cubic centimeters.
† Excluding those treated with ascorbic acid and a patient given a special diet (see text).

TABLE 3.—*Twenty-Four Hour Urinary Excretion of Ascorbic Acid* After Test Dose*

Subjects	Men and Women, Average	Men, Average	Women, Average	Highest Value
11 employees	122.82	101.80	165.98	295.60
18 patients†	11.62	15.26	9.80	24.28

* Values indicate milligrams.
† Excluding those treated with ascorbic acid and a patient given a special diet (see text).

woman after a test dose was 226.11 mg. in twenty-four hours (highest value for a female patient taking the regular diet, 16.04 mg.; average for both sexes, 11.62 mg.).

The lowest values throughout were obtained for the 12 patients segregated for special treatment because of visual disturbance. (This grouping of patients, as of all subjects tested, was done before any tests on excretion or on level in the blood had been carried out.) The second subgroup of these 12 treated subjects, however, indicated a slight general rise in the blood plasma values, apparently coincidental with the seasonal changes in diet, when tested one month later, before treatment was started (table 4).

Studies of the excretion values obtained for all groups without test doses at various times of the day indicated that the ascorbic acid appeared

to be excreted in amounts roughly corresponding to the number of hours during which individual samples were collected. A comparison of the fractional excretion values after the administration of test doses, however, revealed group differences in that the patients, who showed an apparently complete lack of saturation or of vitamin C reserves, maintained about the same ratio of excretion as without the test dose, whereas the employees as a whole excreted more ascorbic acid during the seven hours from 8 a. m. to 3 p. m., i. e., immediately after ingestion of the test dose, than during the next seventeen hours, from 3 p. m. to 8 a. m. the following morning, despite a rather poor response to the test dose as compared with data given in the literature.[28]

The fact that the accuracy of the excretion tests, especially, depended much on the cooperation both of the subjects tested and of

TABLE 4.—*Average Twenty-Four Hour Urinary Excretion of Ascorbic Acid, Level in Blood Plasma and Response to Test Dose for Patients Before Treatment*

Observation	Subjects	Men and Women	Men	Women
Urinary excretion*	Subgroups 1 and 2 (12 patients)	6.35	8.02	5.50
Level in blood plasma, March 16-21, 1938†	Subgroups 1 and 2 (12 patients)	0.45	0.47	0.44
Level in blood plasma, April 23, 1938†	Subgroup 2 (6 patients)	0.55	....	....
Response to test dose‡	Subgroups 1 and 2 (12 patients)	7.11	9.31	5.85

* Values indicate milligrams per twenty-four hours.
† Values indicate milligrams per hundred cubic centimeters.
‡ Values indicate milligrams.

the employees aiding in the collection of specimens was considered; as a rough means of control, the amounts of urine excreted by the various groups in twenty-four hours were measured together with the amounts of ascorbic acid. The general average for all types of employees and patients, comprising about 150 subjects, was thus found to be 1,278 cc.

The values for the vitamin C content of blood plasma obtained before, during and after treatment of the special group of 12 patients are compiled in table 5. It will be noted that, apart from the initial fluctuations encountered when an attempt was made to achieve a maxi-

28. Wright, I. S.; Lilienfeld, A., and MacLenathen, E.: Determination of Vitamin C Saturation: A Five Hour Test After an Intravenous Test Dose, Arch. Int. Med. **60**:264 (Aug.) 1937. Wortis, H.; Liebmann, J., and Wortis, E.: Vitamin C in the Blood, Spinal Fluid and Urine, J. A. M. A. **110**:1896 (June 4) 1938. Abbasy and others.[12] Youmans and others.[21]

mum rise in level in subgroup 1, the values of the blood plasma dropped to a fairly constant high level below that of the initial rise in 10 of the 12 patients, despite the fact that the daily amounts of ascorbic acid administered far exceeded the amounts required to maintain a normal

TABLE 5.—*Level of Ascorbic Acid in Blood for Patients Before, During and After Treatment*

Subgroup 1
Week of Treatment

Case No.	Patient	Sex	Age, Yr.	Before Treatment	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	First Week After Treatment
1	M. B.	F	73	0.45	1.90	1.90	1.75	....	2.30	2.20	1.80	1.80	1.50
2	E. Ba.	F	64	0.44	2.80	1.90	2.20	....	2.50	2.55	2.25	1.80	1.55
3	M. Ho.	F	42	0.43	2.40	2.25	2.20	....	2.75	2.00	2.35	2.20	1.65
4	M. Ha.	F	56	0.40	2.40	2.20	2.15	....	2.60	2.15	2.10	1.75	1.55
5	R. J.	M	38	0.41	1.40	1.45	1.60	....	2.00	1.55	1.75	1.75	1.20
6	G. B.	M	54	0.60	2.00	0.75	1.80	....	1.15	1.85	1.80	1.70	1.40
Average				0.46	2.15	1.74	1.95	....	2.22	2.05	2.01	1.83	1.47

Subgroup 2
Week of Treatment

Case No.	Patient	Sex	Age, Yr.	Before Treatment	First	Second	Third	Fourth	First Week After Treatment
7	E. Bo.	F	41	0.40	....	....	....	0.55	2.55	2.35	1.85	2.00	1.55
8	I. H.	F	47	....	....	....	....	0.50	....	2.20	1.75	1.40	0.80
9	H. M.	F	63	0.48	....	....	....	0.60	2.50	2.10	1.75	1.95	1.70
10	S. B.	F	56	0.46	....	....	....	0.54	1.90	1.80	1.75	1.50	(1.30)*
11	H. J.	M	64	0.47	....	....	....	0.58	2.40	2.20	1.70	(1.20)†	(0.90)†
12	J. C.	M	55	0.40	....	....	....	....	0.95	1.85	1.70	1.50	1.40
Average				0.44	....	....	....	0.55	2.06	2.08	1.75	1.67	1.36
General Average				0.45	....	....	....	....	2.15	2.07	1.88	1.76	1.43

* Treatment continued during fifth week; not included in average.
† No treatment during fourth week; not included in average.

level in the blood and in the urine. That this apparent inability to maintain the maximum attainable level in the blood for more than a short period was, moreover, not due to decreased absorption in the gastrointestinal tract is indicated by the values for urinary excretion obtained for 11 of the 12 patients at the end of the eighth (fourth) week of treatment (table 6), which show a tremendous spilling over of ascorbic acid, practically equivalent, in fact, to the daily dose administered in tablet form.

The twenty-four hour urinary excretion of ascorbic acid was again tested immediately after the final manifest readings of visual acuity for this group, or about eleven days after termination of treatment. The values obtained are included in table 6. It will be noted that the patients differed little from one another in their excretion as tested at any one time, either toward the end of treatment or a fortnight later, but it may be seen also that the values obtained at the latter time are throughout equivalent only to the lower limit of normal daily excretion during a well balanced dietary regimen. That is to say, within eleven days of administration of excessive amounts of the vitamin, with evidence of high values in the blood plasma, the urine failed to show any evidence of an excess of the substance in the body. This indicates the presence of reserve depots in the body; Wortis, Wortis and Marsh [20] have most recently stressed the fact that certain parts of the central nervous system, as well as related structures (pituitary gland, crystalline lens and aqueous humor of the eye and adrenal glands), have been definitely found to contain relatively large amounts of ascorbic acid independent of the level in the blood.

Regardless of the date of the last tests for visual acuity all patients in the treated group were examined at the same time for reading ability and with the ophthalmoscope shortly before beginning treatment; those in subgroup 1 were reexamined after four weeks of treatment; those in subgroups 1 and 2 were examined two weeks later, again at the conclusion of the treatment and finally about eleven days after treatment had been discontinued.

Of the 12 patients thus studied, 1 man and 1 woman could not be included in a final consideration of the effects of treatment because of their psychotic condition. All of the remaining 10 showed some degree of opacity in the vitreous, and 5 showed beginning, moderately advanced or mature cataracts. Other findings were, in some instances, unusually pale disks and narrowed, somewhat tortuous retinal arteries.

Of the 5 patients primarily showing changes of the lens, 4 showed no improvement whatsoever, either of the ophthalmoscopic picture or of visual acuity as determined by manifest readings. The fifth, patient 10 (S. B., table 5), a 56 year old woman, had already undergone an operation for removal of the left lens and showed beginning cataract of the right lens. The left vitreous in particular, however, showed opacities also. Treatment apparently produced no change in the condition of the remaining lens but did affect the opacities of the vitreous, with improvement of vision in both eyes (table 7).

The remaining 5 patients showed improvement of vision (table 7), but it is worthy of note that before treatment the outstanding ophthal-

moscopic findings in these cases were changes in the fundus and in the vitreous and that the latter changes regressed under treatment to a remarkable extent, with complete clearing in some instances.

Associated with these objectively determinable changes under treatment was subjective improvement of vision, expressed by such statements as these: "My eyes are stronger"; "I can do my needle work without my glasses now"; "I can read much easier"; "Things seem so much clearer than they did." Moreover, both objective and subjective improvement set in rapidly when it occurred at all and in most cases did

TABLE 6.—*Twenty-Four Hour Urinary Excretion of Ascorbic Acid* for Patients During and After Treatment*

Time of Determination	Average	Highest Value
Last week of treatment	323.21	356.13
11 days after treatment	16.30	28.88

* Values indicate milligrams.

TABLE 7.—*Manifest Readings of Visual Acuity for Patients Treated Before, During and After Treatment* *

Case No.†	Patient	Sex	Age, Yr.	March 15	April 19 or Later	May 31
4	M. Ha.	F	56	O. D. 20/70 O. S. 20/70	O. D. 20/40 O. S. 20/40	O. D. 20/40+2 O. S. 20/40
6	G. B.	M	54	O. D. 20/00 O. S. 20/70	O. D. 20/00 O. S. 20/50	O. D. 20/200 O. S. 20/50
7	E. Bo.	F	41	O. D. 20/70 O. S. 20/50—1	O. D.‡ 20/40—1 O. S. 20/40—2	O. D. 20/30—2 O. S. 20/30—2
10	S. B.	F	56	O. D. 20/70+2 O. S. 20/00	O. D.‡ 20/40—2 O. S. 20/200+1	O. D. 20/50+1 O. S. 20/100+1
11	H. J.	M	64	O. D. 20/200 O. S. 20/200	O. D.‡ 20/100+1 O. S. 20/200+2	O. D. 20/70 O. S. 20/70—1
12	J. C.	M	55	O. D. ? O. S. ?	O. D.§ 20/40+2 O. S. 20/30—2	O. D. 20/30—1 O. S. 20/30

* One test not included.
† Numbers same as in table 5.
‡ Tested May 7.
§ Tested May 15.

not progress much after two weeks of daily treatment. The last examination, made about eleven days after completion of several weeks of treatment, showed only occasional further changes of note.

As the 2 patients eliminated from this series were originally included in subgroup 1, only 4 subjects in this subgroup were actually considered in these comparisons. Of these, 2, or 50 per cent, reacted favorably to treatment. In subgroup 2, 4 of 6, or 66 per cent, reacted favorably to treatment. This subgroup received only half as much ascorbic acid as subgroup 1; the patients were distributed within the two subgroups as evenly as possible in regard to both age and ophthalmologic findings.

A comparison of the average ages of the patients whose vision improved with those in whom it was unimproved indicates that the older the person, the less favorable the reaction, as the subjects whose condition improved showed an average age of 54.3 years, as against 61.8 years for those whose status remained unimproved. It should be noted, however, that among the most strikingly benefited persons was a patient 64 years old.

All patients were questioned at regular intervals concerning the general state of appetite, sleep, elimination, etc. In the majority of cases the responses were favorable, in some cases remarkably so, especially in regard to mood and appetite. One patient in particular (patient 11, H. J., table 5), a 64 year old man, suffered severely from pains in all large joints and in the spine, with marked initial stiffness on arising from bed or after sitting in one position for any length of time. After the first week of treatment this patient spontaneously offered the information that the initial stiffness had diminished considerably and that the pains in the joints were definitely less troublesome. Throughout the remainder of the treatment and subsequently he has repeatedly made the statement that he feels "better in every way than for the past two years." This feeling of general well-being can probably be ascribed in great part simply to the relief from the constant articular pains. This effect of the administration of ascorbic acid seems, moreover, to be in accordance with recent reports on the manifestations of various degrees of vitamin C deficiency.[29]

It was observed also that in determination of the vitamin levels in the blood plasma the punctured veins, which had, especially in the older members of the group, shown a tendency to bleed rather profusely after venipuncture, gradually improved in this respect to a remarkable degree.

Four of the 12 patients comprising the treated group were inmates of epileptic wards and were receiving either phenobarbital or phenobarbital and bromides at the time this investigation was carried out. The medication apparently had no effect on the reaction to ascorbic acid, for the number and character of the seizures experienced by these patients in the course of the year revealed no demonstrable change during ascorbic acid therapy.

SUMMARY

Various groups of the employee and patient population of the Hastings State Hospital were tested for the twenty-four hour urinary excretion of ascorbic acid, the level of the substance in the blood

29. Rinehart, J. F.; Greenberg, L. D.; Baker, F.; Mettier, S. R.; Bruckman, F., and Choy, F.: Metabolism of Vitamin C in Rheumatoid Arthritis, Arch. Int. Med. **61**:537 (April) 1938. Booth and Hansen.[10b]

plasma and the twenty-four hour excretion after a peroral test dose of 600 mg. of pure ascorbic acid in tablet form. The tests were all carried out during the late winter months of 1938. The findings differed among the different groups; they indicated definite vitamin C deficiency for the patients in general.

For a control group of persons not connected with the institution the levels in the blood plasma were determined in March and May 1938, the test at the latter time coinciding with termination of treatment at this institution. The findings corresponded in the main with those given in the literature for normally nourished subjects.

All the described tests were performed also on a special group of patients who presented visual disturbances due apparently to changes in the tissues associated with aging of the eye. These patients were subjected, in addition, to ophthalmoscopic examination and to reading tests. The findings indicated an even more marked vitamin C deficiency in this group than among the other institutional patients.

The special group was divided into two subgroups, one of which received massive daily doses of ascorbic acid by mouth for eight weeks, while the other received the same medication for four weeks.

Determinations of the levels of reduced ascorbic acid in the blood plasma were carried out at regular intervals during treatment and one week after it, in addition to ophthalmoscopic and reading tests. The twenty-four hour urinary excretion was determined during the last week of treatment and again two weeks later, immediately after the final examination for visual acuity. The findings indicated improvement of eyesight in all patients not suffering primarily from senile cataract. The general well-being of the patients under treatment appeared to be beneficially affected as well.

All findings are recorded in tabular form and briefly discussed, with mention of incidental observations not directly related to the problem under consideration. Sixty per cent of the treated group as a whole showed improvement, as measured by reading test, ophthalmoscopic examination and the subjective reactions of the patients. The results indicated, moreover, that marked improvement sets in within the first two weeks of treatment, if it occurs at all, with slow progression or no further change from then on. Cataracts were apparently not affected by this method of treatment, all improvements being due to clearing of the other optic media and apparently even to some degree to a beneficial effect on the retinal vessels and the head of the optic nerve (or the optic nerve as a whole?). Whether the latter findings represented a direct or an indirect action of ascorbic acid is still a matter of conjecture, although reports of recent work indicate that a direct effect is probable.[20]

CONCLUSIONS

From a comparison of the excretion values and the levels in the blood during and after treatment as well as from the results of ophthalmoscopic and reading tests, it appears that ascorbic acid deficiency can be held at least partly responsible for impairment of vision associated with senescence of the human eye and that the administration of ascorbic acid by mouth in adequate doses can counteract this process, so far as the crystalline lens is not primarily involved.

The lens, although showing a definitely subnormal ascorbic acid content with cataractous conditions, apparently cannot be favorably affected by the administration of ascorbic acid by mouth, even in excessive amounts, after senile changes have set in.

The findings here reported also indicated that little is gained by continuing the administration of large amounts of ascorbic acid if there is no measurable improvement after daily treatment for two weeks. This time limit is liberal.

The fact has not been lost sight of that a method of treatment properly combining more than one of the vitamins known to be specifically associated with the metabolic functioning of the eye may prove successful when ascorbic acid alone ceases to be of benefit.

The Henry Ford Hospital.

All manifest readings of visual acuity were carried out by Dr. D. M. Judkins-Davies, of the medical staff of Hastings State Hospital, who first suggested a possible connection between vitamin deficiency and the condition of the optic media of the patients at this institution and who was in close cooperation with me during the testing of the various groups.

Dr. E. C. Foote, of the Foote Clinic, Hastings, Neb., was ophthalmologic consultant.

The ascorbic acid used in these tests was furnished by the Department of Clinical Research of the Abbott Laboratories, North Chicago, Ill.

EFFECT OF BREATHING GASES UNDER POSITIVE PRESSURE ON LUMENS OF SMALL AND MEDIUM-SIZED BRONCHI

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AND
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A constriction in any part of the air passages from the glottis to the alveoli causes an additional resistance to the passage of air. This results in an increased effort on the part of the respiratory musculature to ventilate the lungs. When obstruction is present within the thorax, respiration modifies the degree of obstruction, since the lumens of the bronchi enlarge on inspiration and constrict during expiration.[1] This variation in size of the smaller bronchi has been demonstrated by roentgenograms of the lungs, made after injection of iodized poppyseed oil.[2] In the extrathoracic trachea and larynx, however, the lumen is not exposed to varying intrathoracic pressures; it is, moreover, protected from alteration in its size by strong cartilaginous rings.

In asthmatic dyspnea, inspiration is short and forcible, and expiration is prolonged. The long-drawn-out character of expiration may be explained by the constriction of the bronchi during the expiratory cycle; a powerful expiratory effort might produce an even greater narrowing of the smaller bronchi and further delay the egress of air. In previous reports of one of us therapy by inhalation under positive pressure of 2 to 7 cm. of water has been described in the treatment of severe asthma and acute pulmonary edema.[3] In obstructive dyspnea the intrapleural

From the Department of Medicine and the Department of Roentgenology, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.

1. Jackson, C., and Jackson, C. L.: Bronchoscopy, Esophagoscopy and Gastroscopy: A Manual of Peroral Endoscopy and Laryngeal Surgery, ed. 3, Philadelphia, W. B. Saunders Company, 1934.

2. Macklin, C. C.: The Dynamic Bronchial Tree, Am. Rev. Tuberc. **25**:393 (March) 1932.

3. Barach, A. L.: (*a*) The Therapeutic Use of Helium, J. A. M. A. **107**: 1273 (Oct. 17) 1936; (*b*) Recent Advances in Inhalation Therapy in the Treatment of Cardiac and Respiratory Disease: Principles and Methods, New York State J. Med. **37**:1095 (June 15) 1937. (*c*) Kernan, J. D., and Barach, A. L.: Rôle of Helium in Cases of Obstructive Lesions in the Trachea and Larynx, Arch. Otolaryng. **26**:419 (Oct.) 1937. (*d*) Barach, A. L.; Martin, J. D., and Eckman, M.: Positive Pressure in the Treatment of Pulmonary Edema, Ann. Int. Med. **12**:754 (Dec.) 1938.

negative pressure is increased during the inspiratory cycle. When air, oxygen or a mixture of helium and oxygen is breathed under a positive pressure of approximately 5 cm. of water, the pathologically elevated negative pressure within the chest is diminished, and dyspnea is alleviated.

During the expiratory cycle the employment of positive pressure appeared to have the advantage of an internal distending force within the tubules of the respiratory passageway, which tended to diminish their constriction during expiration. Evidence for this belief was found in the behavior of patients with continuous asthmatic dyspnea of mild or moderate degree. Breathing under a positive pressure of 2 to 5 cm. of water frequently resulted in a disappearance of many of the rales heard during expiration and in subjective relief. Patients who were taught to purse their lips during expiration, thus creating a pressure which was reflected backward into the lungs, often observed a clearing of the wheezing sounds previously heard. This might in part

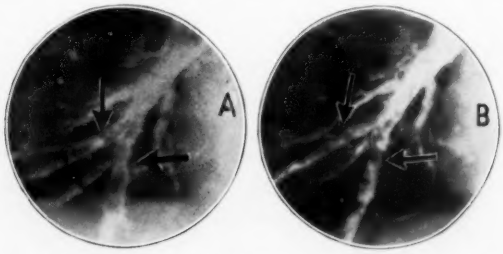

Fig. 1.—*A*, a branch of the bronchial tree after injection of iodized poppyseed oil at the end of inspiration. *B*, a branch of the bronchial tree after injection of iodized poppyseed oil at the end of expiration.

have been due to a decrease in the velocity of air. It seemed desirable, therefore, to test the hypothesis that positive pressure accomplished a relative increase in the diameters of the smaller bronchi during the expiratory cycle, since, if this were true, it would make for more uniform and efficient emptying of the alveoli.

METHODS

Seven patients with varying degrees of asthmatic dyspnea were given intratracheal injections of iodized poppyseed oil. Roentgenograms of the chest were taken at the end of inspiration and of expiration, before and during the inhalation of air under a positive pressure. The apparatus consisted of a motor blower unit, a 1 inch (2.5 cm.) rubber tube, a T tube which made connection to the patient by means of a mouthpiece and a second rubber tube, which led from the patient into a water bottle. The distance to which the expiratory tube was immersed in water represented the pressure obtained during expiration. The pressure used was 5 cm. of water at the end of inspiration and 8 cm. at the end of expiration.

RESULTS

The effect of inspiration and expiration on the size of a branch of the bronchial tree during an attack of asthma of moderate degree is shown in figure 1. Comparison of the widths of the bronchi to which the arrows point reveals a distinct narrowing during the expiratory cycle.

In the 7 patients in whom the effect of positive pressure was studied no consistent changes were observed at the end of inspiration. In 2, the diameters of the bronchi appeared larger when positive pressure was used at the end of inspiration. However, at the end of expiration the widths of the branches of the bronchial tree studied roentgenographically showed a consistent increase when positive pressure was employed. In figure 2 a comparison of the results obtained in a patient with asthma at the end of expiration with and without positive pressure may be seen. It will be observed that the smaller bronchi showed an enlargement of 1 mm. in diameter and the moderate-sized bronchi 2 mm. in diameter when expiration was conducted under positive pressure.

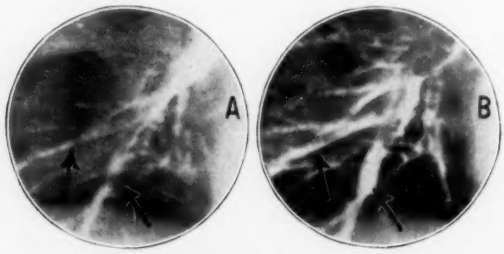

Fig. 2.—*A*, a branch of the bronchial tree after injection of iodized poppyseed oil, at the end of expiration with the patient breathing air without pressure. *B*, a branch of the bronchial tree after injection of iodized poppyseed oil, at the end of expiration with the patient breathing air under positive pressure.

CONCLUSIONS

The effect of breathing air under positive pressure on the size of a branch of the bronchial tree was studied by means of roentgenograms of the chest after injection of iodized poppyseed oil in a series of 7 patients during an attack of mild or moderate asthma. The widths of the small and the moderate-sized bronchi were approximately 1 to 2 mm. larger at the end of expiration when positive pressure was used.

These studies appear to confirm previously reported evidence that breathing atmospheres under positive pressure possesses the physiologic advantage of maintaining a larger bronchial lumen, especially during the expiratory cycle, and thus promoting a more efficient emptying of the alveoli of the lungs.

MANIFESTATIONS OF TRICHINIASIS IN THE CENTRAL NERVOUS SYSTEM

REPORT OF A CASE WITH LARVAE IN THE SPINAL FLUID

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Trichiniasis has been known to involve the central nervous system since 1906, when Frothingham[1] first demonstrated the larvae of Trichinella spiralis in a human brain. Since that time 24 cases have been reported in which the central nervous system has been definitely involved. In spite of this ever increasing evidence, the fact that the larvae do invade the central nervous system and cause symptoms is not generally appreciated. Textbooks rarely mention it.

Recently I had the privilege of observing and following a case of encephalitis due to trichiniasis, with recovery. Larvae were isolated from the spinal fluid. This case is reported in detail, with a brief review of the literature.

REPORT OF CASE

History.—L. T., a white man aged 25 years, was admitted to the contagious division of the University Hospital on April 4, 1938, in a comatose state. The history, as obtained from relatives, was that the patient had been apparently well until about March 20, 1938, at which time he noted fatigue, drowsiness and "rheumatism" in the right arm. A day or so later a rash developed on both forearms, described as being made up of small red spots surrounded by larger red blotches about 1 cm. in diameter. The rash disappeared several days after the application of a lotion. Although the patient was drowsy and slept at every opportunity, he continued his daily occupation of feed grinding in a rural community.

On April 2, 1938, ten days after the onset of fatigue and drowsiness, he was observed to have a staggering gait and to stumble over chairs when he walked about the house. He slept most of that day and by evening was incontinent of urine and of feces. He could be aroused only with great difficulty. On the following day he did not respond to environmental stimuli, which included loud calls, given in an attempt to arouse him. He entered the hospital in this condition.

There was no history of chills, fever, nausea, vomiting or diarrhea. There was no puffiness of the eyelids or injection of the conjunctiva. There were no convulsions.

From the contagious division of the Department of Pediatrics and Infectious Diseases of University Hospital.

1. Frothingham, C.: A Contribution to the Knowledge of the Lesions Caused by Trichina Spiralis in Man, J. M. Research **15**:483-490 (Dec.) 1906.

Within two weeks after his admission to the hospital, the patient's mental state had improved sufficiently for him to give coherent answers to questions. With considerable interrogation the following information was obtained: Three or four days prior to the development of the "rheumatism" in the right arm, the patient had purchased half a pound of sausage and had eaten it uncooked. None of it was taken home to the rest of the family. He vaguely remembered the rash on the forearms, but beyond that all was confusion until he regained complete consciousness three weeks later.

Physical Examination.—The patient was well developed and well nourished. He was in a comatose state. Though he did not respond to questions, he did react to painful stimuli by reflex defense movements. There was no respiratory distress or cyanosis. The rectal temperature was 99 F., the respiratory rate 18 and the pulse rate 80. The skin was dry and of normal color, and there were no eruptions. There was no edema of the eyelids. The pupils were widely dilated, regular and equal; they reacted sluggishly to light. There was transient divergent strabismus. Funduscopic examination of the right eye revealed the disk and the surrounding retina to be edematous, with a crescentic patch of exudate about 3 mm. long just above and temporal to the disk. There was a slight perivascular change along the superior temporal vein. There were no hemorrhages. Funduscopic examination of the left eye showed slight edema of the disk and of the surrounding retina but no hemorrhages or exudates.

The ears and the nose were normal. There was poor oral hygiene and the pharynx was mildly injected. There was no rigidity of the neck. The heart and the lungs were normal. The blood pressure was 105 systolic and 80 diastolic. There was no edema or deformity of the extremities. The upper extremities presented definite rigidity on the right, with some increase of muscle tone on the left; the deep reflexes were equal and active. The abdominal and the cremasteric reflexes were present and equal. The lower extremities showed no disturbance of muscle tone and no weakness. The knee jerk reflexes were present and equal. The achilles tendon reflexes were increased with bilateral ankle clonus, exhaustible on the left and inexhaustible on the right. There was a definite Babinski reflex on the right, a less definite one on the left. The patient reacted to painful stimuli over the entire body.

Initial Laboratory Observations.—Examination of the urine gave results entirely negative. Examination of the blood on April 5, 1938, revealed: hemoglobin, 95 per cent; red cells, 4,980,000, and white cells, 7,800, with polymorphonuclears 50 per cent, eosinophils 38 per cent, lymphocytes 12 per cent, and monocytes and basophils, none. The Kahn test of the blood was negative. The sugar content of the blood was 78 mg. and the nonprotein nitrogen content 42 mg. per hundred cubic centimeters.

Lumbar puncture on admission yielded a clear, colorless fluid under normal pressure. The cell count was 10 lymphocytes per cubic millimeter. The Pandy test was negative. The sodium chloride content was 686 mg. and the sugar content 55 mg. per hundred cubic centimeters. The colloidal gold and the Kahn test were negative. Repeated examinations of the stools showed nothing of importance.

Course.—Owing to the comatose condition of the patient, he was restrained and given intravenous fluids for several days. Three days after his admission to the hospital he was beginning to respond. His eyes would follow a light, and he would nod or shake his head in response to questions. Ten days after admission he was able, with difficulty, to carry on a conversation, and at this time he told of having eaten raw sausage. On two occasions urine pooled from the specimens

of three days failed to show any lead, arsenic or mercury. Biopsies of the right deltoid and the right biceps muscle, taken on April 15 and on April 19, respectively, showed patchy and active chronic myositis. There was necrosis of scattered muscle fibers with adjacent lymphoid infiltrations. Eosinophilic leukocytes were present in moderate numbers. No free or encysted larvae were found. On April 7 and 14 cutaneous tests with trichina antigen, using 0.1 cc. of a 1: 10,000 solution, were negative.

Lumbar punctures were repeated on April 27 and April 28. The physical and chemical findings were essentially the same as those recorded on admission. These later specimens, however, were centrifuged. Two sluggishly motile larvae of T. spiralis were isolated from the fluid drawn on April 27 and one actively motile larva from that obtained on April 28. Hanging drop preparations were made, and microscopic moving pictures were taken of the motile larvae.

The patient's general condition steadily improved. At the time of discharge, on April 30, he was alert and mentally clear. However, he did not have normal control over his arms and legs, and his writing was scarcely legible. The right

Results of Examinations of the Blood in a Case of Encephalitis Due to Trichiniasis

Date	Hemoglobin, per Cent	Red Blood Cells, per Cu. Mm.	White Blood Cells, per Cu. Mm.	Polymorphonuclears, per Cent	Basophils, per Cent	Eosinophils, per Cent	Lymphocytes, per Cent	Monocytes, per Cent
4/ 5/38	95	4,980,000	7,800	50	0	38	12	0
4/ 7/38	88	4,600,000	8,800	37	0	45	15	3
4/ 9/38	..	.....	.....	43	0	45	10	2
4/11/38	..	.....	10,800	56	0	32	10	2
4/13/38	97	.....	8,100	57	0	30	13	0
4/18/38	..	.....	7,200	56	1	28	14	1
4/20/38	94	.....	8,400	60	2	27	10	1
4/29/38	..	.....	9,750	55	0	17	24	4

ankle clonus and the positive right Babinski reflex were still present. Both retinas still showed mild edema. On the right there were exudates and a few vitreous opacities.

The accompanying table gives a detailed account of observations on the blood from time to time throughout the patient's stay in the hospital.

NEUROPATHOLOGY

Those changes due to the presence of the larvae of T. spiralis in the brain have been designated as inflammatory, while those due to toxins have been designated as nonspecific. The latter changes are considered the more dangerous and are more common.

The larvae of T. spiralis have been microscopically demonstrated in the brain by Frothingham,[1] Salzer,[2] Hassin and Diamond,[3] Gruber

2. Salzer, B. F.: Trichinosis: Study of an Epidemic of Fourteen Cases of Trichinosis with Cures by Serum Therapy, J. A. M. A. **67**:579-580 (Aug. 19) 1916.

3. Hassin, G. B., and Diamond, I. B.: Trichinosis Encephalitis: A Pathologic Study, Arch. Neurol. & Psychiat. **15**:34-47 (Jan.) 1926.

and Gamper,[4] Pund and Mosteller [5] and Most and Abeles.[6] Portions of the larvae have been demonstrated in the retina by von Herrenschwand.[7] In these cases the brain was usually diffusely congested with punctate hyperemia. The cortex, the basal ganglions, the medulla and the cerebellum contained minute inflammatory foci or nodules usually made up of glia cells, plasma cells, lymphocytes and polymorphonuclear leukocytes, with an occasional endothelial leukocyte. In these nodules the granular parasites were usually found. Nonspecific degenerative changes were also occasionally present.

Cases showing only nonspecific degenerative changes, similar to those seen in patients dying of severe systemic infections, such as typhoid fever and malaria, have been reported by Knorr,[8] Bloch and Hassin,[9] Pavlica,[10] Walker,[11] Filinski [12] and Gordon and his associates.[13] Hassin and Diamond,[3] who observed microscopically the larvae as well as the nonspecific changes, concluded that the latter are due to the combined action of the toxins from the decomposed muscles and the catabolic products of the larvae. They described these changes as being areas of focal encephalomalacia in which are found neuronophagia, satellitosis and an accumulation of lipoids. Bloch and Hassin [9] found the most striking feature in their case to be vacuolation of the tissues of the brain, caused mainly by the enlargement of the perivascular spaces.

Von Herrenschwand [7] reported a case in which the larvae were found in the retina on autopsy. Characteristic accumulations of cells were found along the periphery, mainly in the region of the ora serrata. The

4. Gruber, G. B., and Gamper, E.: Ueber Gehirnveränderungen bei menschlicher Trichinose, Verhandl. d. deutsch. path. Gesellsch. **22**:219-221, 1927.

5. Pund, E. R., and Mosteller, R.: Trichinosis: Demonstration of the Parasites in the Brain, J. A. M. A. **102**:1220-1222 (April 14) 1934.

6. Most, H., and Abeles, M.: Trichiniasis Involving the Nervous System, Arch. Neurol. & Psychiat. **37**:589-616 (March) 1937.

7. von Herrenschwand, F.: Ueber die Beteiligung des Augapfels an der Trichinellen-Einwanderung bei menschlicher Trichinose, Arch. f. Ophth. **119**:374-385, 1927.

8. Knorr, H.: Beitrag zur Kenntnis der Trichinellenkrankheit des Menschen, Deutsches Arch. f. klin. Med. **108**:137-159 (Sept. 30) 1912.

9. Bloch, L., and Hassin, G. B.: Trichinosis Complicated by Encephalitis, M. Rec. **91**:537-540 (March 31) 1917.

10. Pavlica, F.: Pathologisch-anatomisches Bild der kleinen Trichinoseepidemie in Mähren im Jahre 1925, Med. Klin. **23**:167-169 (Feb. 4) 1927.

11. Walker, A. T.: Trichiniasis: Report of an Outbreak Caused by Eating Trichinous Bear Meat in the Form of "Jerky," J. A. M. A. **98**:2051-2053 (June 11) 1931.

12. Filinski, W.: Pathologic Changes in the Central Nervous System in Trichinosis, Polskie arch. med. wewn. **10**:451-457, 1932.

13. Gordon, M. B.; Cares, R., and Kaufman, B.: Encephalitis and Myocarditis in a Fatal Case of Trichinosis: Report of a Case in a Fourteen-Year-Old Girl, J. Pediat. **6**:667-675 (May) 1935.

accumulations were made up essentially of proliferating cells of the capillary walls. There was some hyalinization, and the capillaries were dilated. An inflammatory infiltrate of lymphocytes and polymorphonuclear neutrophils was also noted. Ten such accumulations were examined, and larvae of T. spiralis were found in six of them.

CLINICAL MANIFESTATIONS

Fifteen cases of trichiniasis producing encephalitis or encephalomyelitis with delirium, stupor or coma and neurologic signs indicating a diffuse involvement of the brain and occasionally of the spinal cord have been reported.[14]

Meningitis due to trichiniasis has been reported by Glazier,[15] Gaisböck,[16] Bloch,[17] Van Cott and Lintz,[18] Meyer,[19] Chasanow,[14e] MacDonald and Waddell[20] and Spink and Augustine.[21] Larvae of T. spiralis were isolated from the spinal fluid in some of these cases; in others they were not.

Loss of deep reflexes has frequently been observed in trichiniasis. Merritt and Rosenbaum[14m] reviewed a series of 110 cases in which treatment for trichiniasis had been given at the Boston City Hospital

14. (*a*) Bloch and Hassin.[9] (*b*) Sterling, W.: Les troubles nerveux de la trichinose, Rev. neurol. **1**:435-439 (April) 1925. (*c*) Hassin and Diamond.[3] (*d*) Gruber and Gamper.[4] (*e*) Chasanow, M.: Meningitis bei Trichinose, Deutsche Ztschr. f. Nervenh. **103**:197-205, 1928. (*f*) Salan, J., and Schwartz, B.: Trichinosis with Involvement of the Central Nervous System, J. A. M. A. **90**:611 (Feb. 25) 1928. (*g*) Horlick, S. S., and Bicknell, R. E.: Trichinosis with Widespread Infestation of Many Tissues, New England J. Med. **201**:816-819 (Oct. 24) 1929. (*h*) Pund and Mosteller.[5] (*i*) Walker.[11] (*j*) Filinski.[12] (*k*) Gordon, Cares and Kaufman.[13] (*l*) Spink, W. W.: Cardiovascular Complications of Trichinosis, Arch. Int. Med. **56**:238-249 (Aug.) 1935. (*m*) Merritt, H. H., and Rosenbaum, M.: Involvement of the Nervous System in Trichiniasis, J. A. M. A. **106**:1646-1649 (May 9) 1936. (*n*) Most and Abeles.[6]

15. Glazier, W. C. W.: Report on Trichinae and Trichinosis, Document 84, United States Treasury Department, Marine-Hospital Service, 1881.

16. Gaisböck, F.: Beobachtungen über Trichinose, Wien. klin. Wchnschr. **22**:410-414, 1909.

17. Bloch, L.: Trichinosis: Report of a Case with the Trichinae Larvae in the Spinal Fluid, J. A. M. A. **65**:2140-2141 (Dec. 18) 1915.

18. Van Cott, J. M., and Lintz, W.: Trichinosis, J. A. M. A. **62**:680-684 (Feb. 28) 1914.

19. Meyer, J.: Trichinosis: A Report of Three Cases Simulating Meningitis, with the Findings of Trichinae Larvae in the Spinal Fluid, J. A. M. A. **70**:588-591 (March 2) 1918.

20. MacDonald, E. P., and Waddell, K. C.: An Epidemic of Trichinosis, J. A. M. A. **92**:449-453 (Feb. 9) 1929.

21. Spink, W. W., and Augustine, D. L.: The Diagnosis of Trichinosis, with Especial Reference to Skin and Precipitin Tests, J. A. M. A. **104**:1801-1805 (May 18) 1935.

over a twenty year period. Absence of deep reflexes was noted in 10 per cent of the cases. Chasanow [14e] considered the loss of reflexes in trichiniasis to be caused by actual neuritis. However, Most and Abeles [9] recently reported a case in which there was absence of deep reflexes, and at autopsy there was no evidence of degeneration of the peripheral nerves. They concluded that the loss of reflexes was in some way due to the pathologic changes in the muscles.

Neuroretinitis due to trichiniasis has been reported by several observers. Parker [22] described a case in which there was diffuse edema of both retinas. The retinal veins were full and tortuous, and several small hemorrhages were seen. He considered these changes to be due to an acute toxic state similar to that present in acute nephritis. Salan and Schwartz [14f] reported a case of optic neuritis in which the larvae were found in the spinal fluid. Spink [14i] described a retinal hemorrhage associated with trichiniasis. Diplopia in cases of trichiniasis has been reported by Parker,[22] Sicard [23] and Stoll.[24] Dilatation of the pupils has been noted late in the disease by Glazier,[15] von Herrenschwand,[7] and Van Cott and Lintz.[18]

LARVAE IN THE CEREBROSPINAL FLUID

Larvae of T. spiralis were first isolated from the spinal fluid by Van Cott and Lintz [18] in 1914. Larvae have subsequently been found in the spinal fluid of patients with manifestations of involvement of the central nervous system by Salan and Schwartz,[14f] MacDonald and Waddell,[20] Salzer,[2] Horlick and Bicknell [14g] (autopsy), Meyer,[19] Hassin and Diamond,[8] Prym [25] and von Herrenschwand [7] (autopsy).

Cases in which larvae have been isolated from the spinal fluid in the absence of neurologic signs have been reported by Bloch,[26] Preble,[27] Elliott,[28] Cummins and Carson [29] and Lintz.[30]

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25. Prym, P.: Ueber Trichinose beim Menschen, Centralbl. f. allg. Path. u. path. Anat. **34**:89-94 (Oct. 15) 1923.

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28. Elliott, A. R.: Trichinosis: Report of a Case with Trichinae Larvae in the Spinal Fluid, J. A. M. A. **66**:504-505 (Feb. 12) 1916.

29. Cummins, W. T., and Carson, G. R.: A Case of Trichinosis with Embryo in the Spinal Fluid, J. A. M. A. **66**:1856-1857 (June 10) 1916.

30. Lintz, W.: Trichinosis and the Cerebrospinal Fluid, J. A. M. A. **66**:1856 (June 10) 1916.

A total of 24 cases have been reported in which larvae of T. spiralis have been isolated from the spinal fluid. In 11 of these the patient recovered, and in 4 the patient died during the acute stage of the disease. In 9 cases no report was made as to the final outcome.

The spinal fluid occasionally is under increased pressure. Lymphocytes are usually present, varying in number from 10 to 240 per cubic millimeter. The results of other laboratory examinations of the fluid are usually negative.

Oddly enough there seems to be no definite relation between the presence of larvae in the spinal fluid and the symptoms or signs of involvement of the central nervous system. In the case reported in this paper the larvae were isolated from the spinal fluid during the sixth

Photomicrograph of a trichina larva isolated from the spinal fluid.

week of the disease. There had never been any meningeal signs, and at that time the encephalitic signs had cleared about 75 per cent. In the case reported by Cummins and Carson [29] the larva was isolated from the spinal fluid during the fifth week of the disease. No symptoms of involvement of the central nervous system had been present at any time. Salzer reported a case of a 3 year old girl in which larvae of T. spiralis were found in the spinal fluid three months after clinical recovery.

From these observations it seems logical to infer that the larvae are present in most cases of trichiniasis regardless of the presence or absence of neurologic signs. It might be well to examine a centrifuged specimen of spinal fluid in all cases suspected of being instances of trichiniasis before a biopsy of muscular tissue is made. Lumbar puncture is less complicated, more economical and usually less objectionable to the patient than the biopsy.

COMMENT

The case reported in this paper presents certain features of special interest. The clinical picture at the time of the patient's admission to the hospital was that of toxic encephalitis with neuroretinitis. There were no gastrointestinal symptoms, and no history of edema of the eyelids could be obtained. The temperature was normal throughout the entire course of the disease. Fever is usually so much a part of the picture that trichiniasis and typhoid are frequently confused.

Dilatation of the pupils, mentioned by previous observers, was noted in this case. On the patient's admission to the hospital this feature was so pronounced that I thought he had received atropine drops in the eyes before coming to the hospital.

The eruption on the forearms may or may not have been related to the trichiniasis. Tyzzer [31] stated that a transient scarlatiniform rash is sometimes seen. Elliott [28] reported a case in which "rose spots" were noted on the abdomen.

The larvae were isolated from the spinal fluid during the sixth week of the disease, after most of the symptoms and signs had disappeared. Microscopic moving pictures of these motile larvae, taken by Dr. Harry A. Towsley, demonstrate great activity.

SUMMARY

A case of trichiniasis which presented a clinical picture of toxic encephalitis and neuroretinitis, with subsequent recovery, is reported. Motile larvae were isolated from the spinal fluid after the encephalitic signs had largely disappeared.

Review of the literature reveals that the presence of larvae in the spinal fluid does not always produce clinical manifestations of involvement of the nervous system. Larvae of T. spiralis in the spinal fluid have been reported in 24 cases. Of these, 4 were fatal, a mortality rate of 26.6 per cent.

From the reported cases it seems probable that careful examination of the spinal fluid in suspected cases of trichiniasis, with or without symptoms of involvement of the central nervous system, may aid in the diagnosis of this disease.

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SULFANILAMIDE

A STUDY OF ITS MODE OF ACTION ON HEMOLYTIC STREPTOCOCCI

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In previous studies of the streptococcidal power of whole blood in vitro, it was ascertained that the organisms were killed by intracellular digestion following phagocytosis. In order to render phagocytosis effective, it was necessary to have specific antibody present in the plasma. Plasma without leukocytes was incapable of killing organisms. Tillett [1] has demonstrated that plasma obtained from patients with febrile diseases not due to a hemolytic streptococcus is bacteriostatic, as well as bactericidal, for certain strains of hemolytic streptococci. As a part of our studies on hemolytic streptococcic infections, it was desirable to determine the effect of adding sulfanilamide to whole blood and to plasma in vitro and to study its mode of action. We were especially interested in determining whether the bactericidal power of the blood could be enhanced, since we have shown previously that during the natural course of hemolytic streptococcic infections specific antibodies increased or appeared as a result of the infection.

METHODS

To study the effect of sulfanilamide on the bactericidal action of whole blood, we used the method described by Spink and Keefer.[2] For the experiments samples of blood were obtained from various persons who were free from hemolytic streptococcic infections, because previous experience had taught us that the bactericidal action of whole blood from infected persons is frequently increased above that of control subjects, especially as the disease advances. The same strain of

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Tillett, W. S.: The Bactericidal Action of Human Serum on Hemolytic Streptococci: I. Observations Made with Serum from Patients with Acute Infections and from Normal Individuals, J. Exper. Med. **65**:147, 1937; II. Factors Which Influence the Phenomenon in Vitro, ibid. **65**:163, 1937.

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the hemolytic streptococcus was used in all the tests reported. It was a group A strain that had been isolated from the circulating blood of a patient who died of puerperal sepsis. This strain was selected since it was found that few persons could kill small numbers of these organisms with their blood. The blood was studied for its streptococcidal power with and without the addition of varying amounts of sulfanilamide. When variations from this technic were used it will be so stated.

EFFECT OF ADDING SULFANILAMIDE TO WHOLE BLOOD

To test the effect of sulfanilamide on the growth and the bactericidal power of the blood of various persons, the following plan was followed. A group A strain of the hemolytic streptococcus which had been recently isolated from the circulating blood of a patient with puerperal sepsis was tested against 30 samples of blood from patients without hemolytic streptococcic or other infection. One-half a cubic centimeter of whole defibrinated blood was used with varying numbers

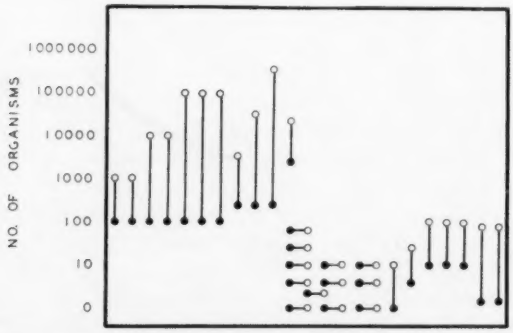

Chart 1.—Bactericidal effect of sulfanilamide in whole blood. The solid dots represent the bactericidal power of 0.5 cc. of whole blood without sulfanilamide; the circles, with sulfanilamide, 10 mg. per hundred cubic centimeters.

of organisms. When sulfanilamide was added to the blood, a freshly prepared 0.8 per cent solution was used so that the final concentration in the blood varied from 2.5 to 10 mg. per hundred cubic centimeters. The number of organisms killed was determined from the number in the tube which failed to show any growth after twenty-four hours in a rotating machine in the incubator.

The first group of experiments was carried out with a concentration of sulfanilamide in the blood equal to 10 mg. per hundred cubic centimeters. The results of the tests are recorded in chart 1. It is seen that the addition of sulfanilamide to whole blood was not in all cases followed by an increase in the bactericidal activity. Indeed, in many instances there was no difference between the bactericidal power of the blood with and that without sulfanilamide, but in no instance did sulfanilamide interfere with the bactericidal action of whole blood. In some cases, however, the number of organisms which were killed definitely increased after the addition of sulfanilamide, and the increase was more striking in the cases in which the blood alone contained bacterial antibodies. It is suggestive, at least, that in the presence of antibodies the addition of sulfanilamide may enhance the bactericidal power of the blood.

EFFECT OF VARYING CONCENTRATIONS OF SULFANILAMIDE IN WHOLE BLOOD

From the foregoing experiments it seemed clear that in some samples of blood, with a concentration of 10 mg. per hundred cubic centimeters, there was an increase in bactericidal power. We had to determine whether varying the concentration of sulfanilamide in these samples of blood would affect the number of organisms that were killed. The same sample of blood, with varying numbers of organisms and different concentrations of sulfanilamide per hundred cubic centimeters of blood, was studied. Two and one-half, 5, 7, 8 or 10 mg. per hundred cubic centimeters was added to the blood. The results are shown in chart 2. In several cases the effect of higher concentrations, i. e., 20, 30 or 40 mg. per hundred cubic centimeters, was studied. It is shown in chart 2 that maximum effects were obtained when more than 5 mg. per hundred cubic centimeters,

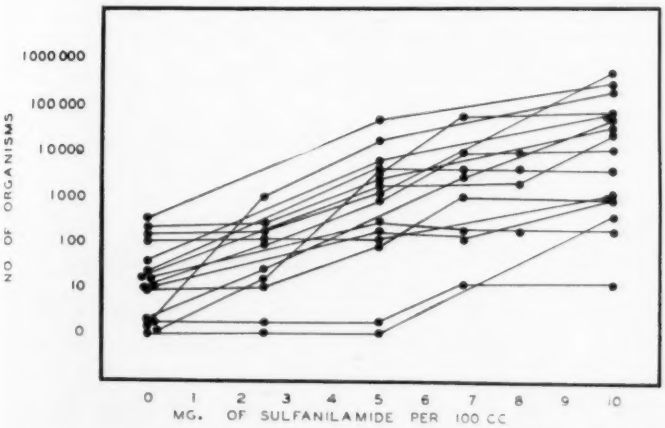

Chart 2.—Bactericidal effect of varying amounts of sulfanilamide on different samples of blood showing bactericidal power.

especially 7 mg. or more, was added. We found no further enhancement of the action when amounts greater than 10 mg. were added to the blood.

These observations indicate that in order to obtain a maximum effect on whole blood in vitro it is necessary to obtain a concentration in the blood of at least 5 mg. per hundred cubic centimeters. The same effects on the bactericidal action of the blood could be demonstrated when the drug was administered by mouth provided the concentration reached 5 mg. or more per hundred cubic centimeters of blood.

EFFECTS ON THE WHOLE BLOOD OF ADMINISTERING SULFANILAMIDE BY MOUTH

To establish whether sulfanilamide when administered by mouth has the same effect on the blood as when added to it in vitro, 7 normal persons were given the drug by mouth so that the concentration in the blood varied from 4.6 to 6

mg. per hundred cubic centimeters; then their blood was tested for bactericidal and bacteriostatic effects. These results are shown in table 1, and it can be seen that the effects were the same whether the drug was given by mouth or added to the blood in vitro; namely, bacteriostasis and bactericidal effects were observed.

EFFECT OF ADDING SULFANILAMIDE TO PLASMA

In previous studies, we were unable to show that blood plasma obtained from normal persons or from patients suffering from nonfebrile diseases is capable of killing various strains of hemolytic streptococci. This was true whether the plasma contained specific antibody or not. As a part of the present investigation,

TABLE 1.—*Effect of Sulfanilamide on Whole Blood After Its Administration by Mouth*

Dilution of Culture	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-7}
Whole blood	∞*	∞	∞	∞	0	0	0	1†
Whole blood plus sulfanilamide, 5.6 mg. per 100 cc.	∞	∞	3,000	0	0	0	0	
Whole blood	∞	∞	∞	∞	0	0	0	1
Whole blood plus sulfanilamide, 5.2 mg. per 100 cc.	∞	∞	∞	∞	20	0	0	
Whole blood	∞	∞	∞	∞	∞	0	0	4
Whole blood plus sulfanilamide, 4.6 mg. per 100 cc.	∞	1,000	10	0	0	0	0	
Whole blood	∞	∞	∞	∞	∞	∞	0	2
Whole blood plus sulfanilamide, 4.8 mg. per 100 cc.	∞	∞	∞	∞	∞	1,000	0	
Whole blood	∞	∞	∞	∞	0	0	0	2
Whole blood plus sulfanilamide, 6 mg. per 100 cc.	∞	∞	0	0	0	0	0	
Whole blood	—	—	∞	∞	∞	∞		2
Whole blood plus sulfanilamide, 5 mg. per 100 cc.	—	—	∞	∞	60	10		
Whole blood	∞	∞	∞	∞	∞	0	0	2
Whole blood plus sulfanilamide, 6 mg. per 100 cc.	∞	∞	200	0	0	0	0	

* Innumerable colonies.
† Total number of organisms in 10^{-7} dilution.

we studied the effect of adding sulfanilamide to plasma and compared the bactericidal action of whole blood and sulfanilamide with that of plasma and sulfanilamide. In all we studied 20 samples of plasma, with and without the addition of sulfanilamide, and in no case were we able to demonstrate a bactericidal effect with the strains employed. The results in 3 cases serve as examples, and they are shown in table 2. In each of the experiments 0.5 cc. of whole blood or 0.5 cc. of plasma was used. One tenth of a cubic centimeter of varying dilutions of organisms was added to each tube, and in the tubes containing sulfanilamide the total concentration of the chemical was equal to 10 mg. per hundred cubic centimeters. The table shows that when whole blood was capable of destroying a certain number of organisms the same capacity could not be demonstrated for the plasma alone. Moreover, the addition of sulfanilamide did not change the capacity of plasma so far as destruction of organisms was concerned.

From these observations one concludes that leukocytes are necessary for the destruction of hemolytic streptococci in vitro even in the presence of sulfanilamide.

We next turned our attention to the problem of bacteriostasis when organisms were added to plasma. After the addition of a measured number of organisms to blood plasma, the total number of organisms present at the end of two, four, eight, ten and twenty-four hours was determined in samples of plasma, with and without sulfanilamide. The results of an experiment which was typical are illustrated in chart 3. It was found that there were fewer organisms at the end of twenty-four hours in the sample of plasma containing sulfanilamide than in the sample without it. This indicates that there was some decrease in the rate of multiplication of organisms in the presence of sulfanilamide, but it was less striking than when whole blood was used.

TABLE 2.—*Effect of Adding Sulfanilamide to Whole Blood and Plasma*

Dilution of Organisms	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-7}
Patient 1	..	..	..	..	..	..	..	10*
Whole blood	+†	+	0‡	0	0	0	0	
Whole blood plus sulfanilamide	+	+	+	0	0	0	0	
Plasma	+	+	+	+	+	+	+	
Plasma plus sulfanilamide	+	+	+	+	+	+	+	
Patient 2	..	..	..	..	..	..	..	10
Whole blood	+	+	+	0	0	0	0	
Whole blood plus sulfanilamide	+	+	+	0	0	0	0	
Plasma	+	+	+	+	+	+	+	
Plasma plus sulfanilamide	+	+	+	+	+	+	+	
Patient 3	..	..	..	..	..	..	..	10
Whole blood	+	+	+	0	0	0	0	
Whole blood plus sulfanilamide	+	+	+	0	0	0	0	
Plasma	+	+	+	+	+	+	+	
Plasma plus sulfanilamide	+	+	+	+	+	+	+	

* Total number of organisms in 10^{-7} dilution.
† + = growth after 24 hours.
‡ 0 = no growth after 24 hours.

These experiments with plasma in vitro seem to indicate that sulfanilamide reduces the rate of multiplication of hemolytic streptococci, but there is no evidence of a bactericidal effect. They also emphasize the importance of cells in destroying hemolytic streptococci in vitro.

STUDY OF THE BACTERIOSTATIC EFFECT OF SULFANILAMIDE

Since the bactericidal effect of sulfanilamide varied in different samples of whole blood, we had to determine whether or not the drug exerted a bacteriostatic effect in the samples in which it was not possible to show that the blood was sterilized. Two methods were used to study this problem. In the first, parallel series of tubes containing 0.5 cc. of whole blood were seeded with varying numbers of organisms. One series of tubes contained sulfanilamide; the other did not. These tubes were sealed and placed in a rotating machine in the incubator for twenty-four hours. At the end of that time the tubes were opened, and the total number of organisms in them was determined by means of pour plates. Eighteen samples of blood were studied in this way, with the use of strain C, and the results are shown in chart 4.

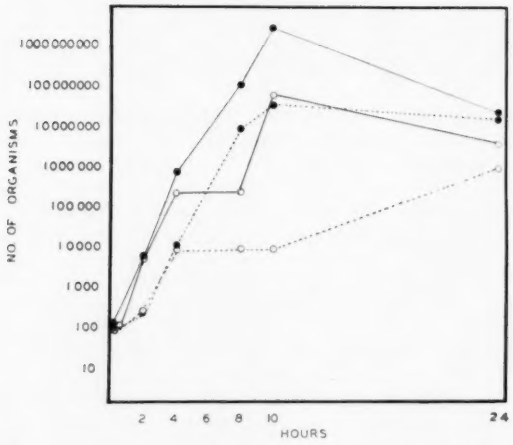

Chart 3.—Comparison of the bacteriostatic effect of sulfanilamide in whole blood and in blood serum. The broken line with solid dots represents blood; the solid line with solid dots, serum; the broken line with circles, blood with 10 mg. of sulfanilamide per hundred cubic centimeters, and the solid line with circles serum with 10 mg. of sulfanilamide per hundred cubic centimeters.

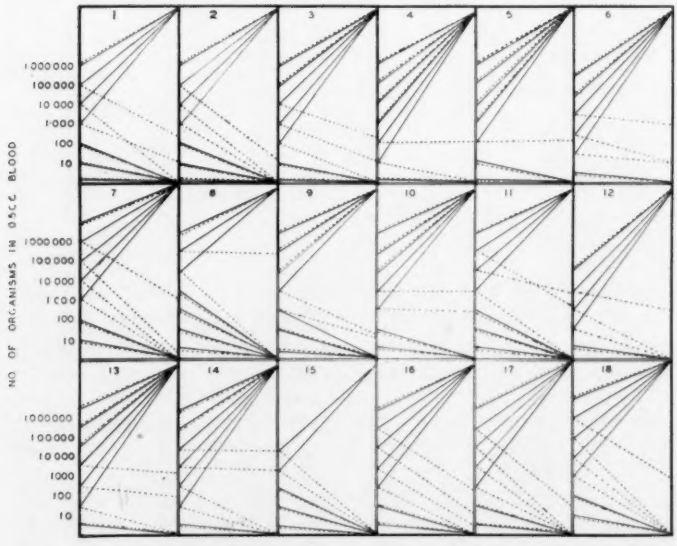

Chart 4.—Bactericidal and bacteriostatic effect of sulfanilamide (10 mg. per hundred cubic centimeters) in 18 different samples of whole blood with strain C. The solid lines represent whole blood; the broken lines, whole blood and sulfanilamide. The lines on the left of each square indicate the total number of organisms in 0.5 cc. of blood. The points on the right of each square indicate the total number at the end of twenty-four hours. The point in the upper right hand corner of each square indicates infinity. The point in the lowest corner of each square indicates no growth.

The second method of studying bacteriostasis was to determine the growth at varying intervals after the inoculation of organisms into the blood. That is to say, the total number of organisms in the blood with and in that without sulfanilamide was determined two, four, eight, ten and twenty-four hours after incubation. The results are recorded in chart 5. In every case there was a decrease in the rate of reproduction of hemolytic streptococci when sulfanilamide was added to the blood, and in some instances the organisms failed to grow after twenty-four hours' incubation.

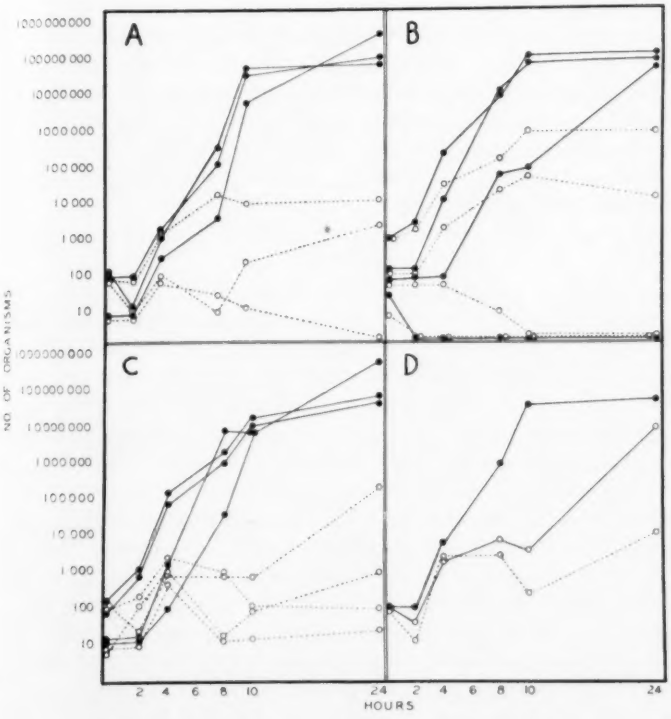

Chart 5.—*A*, *B* and *C*, bacteriostatic effect of sulfanilamide (1 mg. per hundred cubic centimeters) on whole blood with varying numbers of organisms in 3 subjects. The solid line represents blood; the broken line, blood with sulfanilamide. *D*, difference between the effects with 5 and with 10 mg. per hundred cubic centimeters. The solid line with solid dots represents blood; the broken line, blood with 10 mg. of sulfanilamide, and the solid line with circles, blood with 5 mg.

When the results of adding 5 and 10 mg. per hundred cubic centimeters, respectively, were studied (chart 5), it was found that the inhibition of growth was somewhat greater with 10 than with 5 mg.

These experiments show that when sulfanilamide is added to whole blood in vitro so that the concentration is 10 mg. per hundred cubic centimeters of blood there is bacteriostasis in every case. In some samples of blood it was possible to demonstrate a bactericidal effect that was greater when sulfanilamide was added than it was with the whole blood alone. This was more striking when the blood contained bactericidal properties without sulfanilamide and when small numbers of organisms were used.

In the instances in which there was an inhibition of growth, two phenomena were observed: 1. When small numbers of organisms were used there was often no evidence that multiplication took place, but the organisms were capable of reproduction when they were subcultured to mediums containing no sulfanilamide. 2. The inhibition was effective in increasing the lag phase, and the total number of organisms at the end of twenty-four hours was smaller in blood containing sulfanilamide than in whole blood without it.

COMMENT

The objective in the treatment of hemolytic streptococcic infections is to suppress the growth of organisms, prevent their spread from the point of invasion and, finally, destroy them completely. In the natural sequence of events this is accomplished by the summation of a number of factors, such as local inflammation, the presence of specific antibodies and active and viable phagocytes. There seems to be evidence available that sulfanilamide in the tissue fluids inhibits and reduces the growth and rate of multiplication of hemolytic streptococci provided the concentration is above 7 mg. per hundred cubic centimeters. There is no evidence that this chemical destroys hemolytic streptococci through its direct action on the organism, nor is it clear that it stimulates either the accumulation of phagocytes or their activity. There is, however, suggestive evidence that in the presence of antibodies more organisms may be destroyed when sulfanilamide is present than when it is not. This may be due to a reduction in the substances which neutralize the antibodies present and those which are being elaborated. On this point more work is needed.

The destruction of hemolytic streptococci in the body is due to a complex process and, as stated, depends in large part on the cooperative activity of a number of factors. The general belief that these organisms are destroyed by intracellular ingestion is well supported by numerous observations in carefully controlled experiments. In the test tube, at least, it can be shown that the destruction of hemolytic streptococci depends on the combined and cooperative action of specific antibody in the plasma and active viable phagocytes. There is good evidence that the

bacteria are sensitized by the antibody and in this way conditioned so that phagocytosis can take place. It is known also that without the presence of antibody the organisms grow freely and elaborate substances which destroy leukocytes (leukocidin) and red blood cells (hemolysin-streptolysin). There is additional evidence that during febrile diseases not due to hemolytic streptococcic infection there is a change in the properties of the blood plasma that inhibits the growth of some strains of organisms. This phenomenon has been studied especially by Tillett.[1] Its importance has not been studied sufficiently thoroughly in cases of human hemolytic streptococcic infection to be assessed relative to the defense mechanism of the body.

To explain the mode of action of sulfanilamide in hemolytic streptococcic infections, the following hypotheses have been proposed: 1. It stimulates phagocytosis. 2. It neutralizes toxins. 3. It acts by inhibiting the growth of organisms. 4. It actually is bactericidal under certain conditions. 5. It delays growth of organisms until mononuclear phagocytes accumulate. 6. The organisms are altered so that phagocytosis can take place.

These various hypotheses merit discussion.

One of the first questions studied was whether sulfanilamide has any effect on the bacteria themselves, that is to say, whether the drug acts on the bacteria and makes them more easily destroyed. Levaditi and Vaisman [3] maintained that streptococci grown in the animal body, and not in culture mediums, when injected into other mice are practically unaffected by prontosil therapy.[4] We have not been able to confirm this with the strains of hemolytic streptococci that we have used to infect mice, since organisms could be transferred from one mouse to another with identical results as far as the effect of sulfanilamide was concerned. Moreover, we found that organisms that were grown in mediums containing sulfanilamide for twenty-four or forty-eight hours were still as capable of producing fatal infections in mice with the same number as organisms that had not been exposed to the drug. In a word, we were not able to find that sulfanilamide changed the organism in such a way that when it began reproducing it failed to invade or produce a fatal infection in mice. Moreover, we were not able to find that such treatment enhanced the virulence of bacteria.

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4. They used the original prontosil, the hydrochloride of 4-sulfamido-2′,4′-diaminoazobenzene.

More recently, however, Meyer [5] has found that growing hemolytic streptococci in a serum medium containing a sulfanilamide-sugar compound causes clumping of the organism, decreases its virulence and inhibits production of toxin.

Lyons [6] reported that hemolytic streptococci which have been grown in serum containing sulfanilamide for fifteen or twenty subcultures are more vulnerable to phagocytosis and are killed in greater numbers by human blood after this procedure than before.

These studies are the first suggesting that the growth of hemolytic streptococci in vitro in the presence of sulfanilamide changes their virulence.

DOES SULFANILAMIDE AFFECT PHAGOCYTOSIS?

Bliss and Long [7] noted increased phagocytosis and a decrease in free cocci in the peritoneal cavities of mice infected with hemolytic streptococci and treated with sulfanilamide. It was not clear whether the decrease was due to stimulation of phagocytosis or to a change in the bacteria that rendered them more susceptible to phagocytosis. That phagocytosis is necessary for killing there is no doubt. The authors stated that the drug does not stimulate phagocytosis or protect the cells from the products of the bacteria. McKinney and Mellon [8] expressed the opinion that phagocytosis is conditioned by the previous bacteriostatic action of the drug. These observations receive indirect support from the studies of Ward and Lyons,[9] who showed that phagocytosis of rapidly growing, young, virulent hemolytic streptococci did not take place without the presence of specific antibody, whereas organisms in the noncapsulated phase or in old cultures were often phagocytosed without the presence of specific antibody. There is evidence, then, that sulfanilamide does not interfere with phagocytosis, although there is no evidence that it stimulates it. There is suggestive evidence that the bacteriostatic effect of sulfanilamide may enable phagocytes to take up more organisms and that in this way their destruction is accomplished.

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8. McKinney, R. A., and Mellon, R.: Sulfanilamide and Macrophage Response to Hemolytic Streptococcal Peritonitis in Mice, Proc. Soc. Exper. Biol. & Med. **37**:333, 1937.

9. Ward, H. K., and Lyons, C.: Studies on the Hemolytic Streptococcus of Human Origin: I. Observations on Virulent, Attenuated, and Avirulent Variants, J. Exper. Med. **61**:515, 1935. Lyons, C., and Ward, H. K.: II. Observations on the Protective Mechanism Against Virulent Variants, ibid. **61**:531, 1935.

Gay and Clark [10] concluded from their studies of experimental hemolytic streptococcic empyema in rabbits that the course of events in their animals treated with sulfanilamide was a bacteriostatic action of the drug, the outpouring of leukocytes and, finally, complete sterilization of the pleural cavity by the monocytes derived from the local tissues. They stated the belief that there is no evidence that the drug stimulates the localization of monocytes. From numerous experiments, they have found that the destruction of the hemolytic streptococci in the pleural cavity of the rabbit is the function of the monocytes but that it requires time for these cells to increase in large number. In the case of an infection due to organisms that are reproducing rapidly, invasion takes place before the infection can be localized and dealt with adequately by the monocytes. Thus its bacteriostatic action is an important function of sulfanilamide.

BACTERIOSTATIC AND BACTERICIDAL EFFECTS

In determining the bactericidal effect of any substance one must take into account that slight changes in culture mediums will often prevent growth of bacteria and that these effects are soon followed by the death of the organism. That is to say, when the environment is changed so that bacteria cannot multiply they often die, so that it is difficult and, indeed, of little value many times to differentiate bactericidal from bacteriostatic effects.

There seems to be general agreement among those who have studied the problem that sulfanilamide in concentrations of 1:10,000 causes a reduction in the growth of hemolytic streptococci in broth and even in the presence of blood serum. In the experience of Long and Bliss [11] this inhibition was effective only in increasing the lag phase of growth after two hours' incubation.

Colebrook, Buttle and O'Meara [12] demonstrated that whole blood or serum is both bacteriostatic and bactericidal when sulfanilamide is added to either in vitro. Moreover, the administration of sulfanilamide by mouth to man or monkeys is followed by a higher bacteriostatic and bactericidal action than that observed in normal blood or serum. These effects were observed only when small numbers of organisms were

10. Gay, F. P., and Clark, A. R.: On the Mode of Action of Sulfanilamide in Experimental Streptococcus Empyema, J. Exper. Med. **66**:535, 1937.

11. Long, P. H., and Bliss, E. A.: Para-Amino-Benzene-Sulfonamide and Its Derivatives: Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcic Infection; Preliminary Report, J. A. M. A. **108**:32 (Jan. 2) 1937.

12. Colebrook, L.; Buttle, G. A. H., and O'Meara, R. A. Q.: The Mode of Action of *p*-Aminobenzene Sulphonamide and Prontosil in Hemolytic Streptococcal Infections, Lancet **2**:1323, 1936.

used. The same workers expressed the opinion that serum containing sulfanilamide kills almost as many organisms as whole blood, and they stated that probably the effect of the leukocytes is to enhance the killing of the cocci by the drug.

The blood of rabbits, guinea pigs and mice is less effective in killing hemolytic streptococci than is human or monkey blood.

Recent studies by Hoare [13] have shown that sulfanilamide has a bactericidal effect when it is added to normal human blood. Our own studies show that sulfanilamide has always exerted a bacteriostatic effect when it is added to whole blood or plasma. This was most striking when concentrations of 7 to 10 mg. per hundred cubic centimeters were used together with small numbers of organisms. We were unable to show that the addition of sulfanilamide to whole blood produced a bactericidal effect in all cases. The variations in the effect were due in part to the presence or absence of antibodies in the samples of normal blood which were used in the tests, and we have recently found that there is considerable variation in the bactericidal effect of the drug when different specific serologic types of streptococci are used.

NEUTRALIZATION OF TOXINS

Osgood and Brownlee [14] have expressed the opinion that the main action of sulfanilamide on the beta hemolytic streptococci is the neutralization of toxins. They stated the belief that the drug does not kill these organisms directly, although the bactericidal properties of normal serum and, to some extent, phagocytosis of organisms by leukocytes are also operative. In their opinion, there is no direct effect on phagocytosis. The slowing of the rate of growth which has been observed by all investigators was attributed to the neutralization of toxins, and the bacteriostasis was interpreted to be probably incidental and not essential.

The evidence for the neutralization of toxins was based on the observation that there was a decrease in the size of hemolyzed areas in blood agar plates about colonies exposed to sulfanilamide. Unfortunately, the authors produced no evidence that filtrates from their cultures caused any destruction in their marrow cultures, either with or without sulfanilamide. Recent work by Gross, Cooper and Lewis [15]

13. Hoare, E. D.: Bactericidal Changes Induced in Human Blood and Serum by Sulphamido-Chrysoidine and Sulphanilamide, Lancet **1**:655, 1938.

14. Osgood, E. E., and Brownlee, I. E.: Culture of Human Marrow: Studies on the Mode of Action of Sulfanilamide, J. A. M. A. **110**:349 (Jan. 29) 1938.

15. Gross, P.; Cooper, F. B., and Lewis, M.: Inhibition of Streptococcal Hemolysis by Sulfanilamide Compounds, Proc. Soc. Exper. Biol. & Med. **38**:275, 1938.

has demonstrated that there was "a slight almost negligible inhibition of the hemolytic activity of streptococcic hemolysin by sulfanilamide." Huntington [16] has also found that the presence of sulfanilamide fails to prevent the production of fibrinolysin or erythrogenic toxin by the growing organism. Osgood and Brownlee [14] suggested further that hemolytic streptococci would resemble a harmless saprophyte and be readily vulnerable to the ordinary defense mechanism of the body provided the toxins were neutralized, destroyed or prevented from forming by the presence of sulfanilamide. We have found that even when there is no reproduction of the organism in vitro there may not be any destruction. This observation suggests that some mechanism other than the neutralization or absence of toxin is necessary for the death of the organism in blood. In the light of existing knowledge concerning the activity of hemolytic streptococci, it is difficult to believe that neutralizing toxin alone ever places them in the category of harmless saprophytes. Indeed, Fothergill and Lium [17] have shown that antistreptococcus serum of high antitoxic value has no effect on the reproduction or the death of virulent streptococci in vitro. We have found in unpublished experiments that addition of erythrogenic toxin to whole blood which was bactericidal caused no demonstrable decrease in the bactericidal properties of the blood.

We can say, however, that we have noted bacteriostasis in tubes in which the organisms had survived but no hemolysis of the blood had taken place, which suggests at least that without reproduction there is no production of hemolysin.

BACTERIOSTASIS IN MICE

From experiments with mice infected with mouse-virulent strains of hemolytic streptococci there seems to be evidence that the main action of the drug is that of bacteriostasis, since death is delayed only as long as the drug is injected.[11]

To study further the effect of sulfanilamide, we observed its action in mice infected with hemolytic streptococci.

Experimental Studies.—We have found, in common with others, that the injection of sulfanilamide into mice which have been infected with a strain of hemolytic streptococcus that is mouse virulent will prevent death as long as the administration of the drug is continued. When it is stopped many of the animals die. Tables 3 and 4 show our results in the treatment of mice. Table 3 indicates

16. Huntington, R. W., Jr.: Failure of Sulfanilamide to Prevent Hemolysis, Fibrinolysis, and Production of Erythrogenic Toxin by Hemolytic Streptococci in Vitro, Proc. Soc. Exper. Biol. & Med. **38**:328, 1938.

17. Fothergill, L. D., and Lium, R.: Value of Commercial, Antibacterial Streptococcus Sera in Hemolytic Streptococcal Infections, New England J. Med. **211**:99, 1934.

that the strain that we used killed mice with regularity when a 10^{-4} dilution of a virulent strain was injected intraperitoneally and in a high percentage of instances when smaller numbers of organisms were injected.

TABLE 3.—*Summary of Results of Injecting Varying Numbers of Hemolytic Streptococci (Strain C-203) into Control Animals*

Dilution of 18 Hour Culture*	Number of Mice Infected	Number of Mice	
		Surviving	Dead
10^{-2}	3	0	3
10^{-3}	21	0	21
10^{-4}	48	0	48
10^{-5}	30	3	27
10^{-6}	5	2	3
10^{-7} †	3	2	1
Total	110	7	103

* Each mouse received 1 cc. of culture dilution.
† 10^{-7} = 20 to 30 organisms per cubic centimeter.

TABLE 4.—*Summary of the Effect of Sulfanilamide on Hemolytic Streptococcic Peritonitis in Mice*

Number of Mice	Culture	Treatment Started After Infection	Total Amount of Drug, Mg.	Days of Treatment	Number of Deaths Days											Summary	
					1	2	3	4	5	6	7	8-11	12-16	17-21	22-30	Survived	Died
3	10^{-2}	—	0	..	3	..	..	..	..	..	..	..	..	..	..	0	3
6	10^{-2}	4 hr.	16	1	6	..	..	..	..	..	..	..	..	..	..	0	6
6	10^{-2}	8 hr.	8	1	6	..	..	..	..	..	..	..	..	..	..	0	6
4	10^{-3}	—	0	0	4	..	..	..	..	..	..	..	..	..	..	0	4
12	10^{-3}	Immediately	125	7	..	..	..	1	..	..	..	6	2	..	..	3	9
4	10^{-3}	4 hr.	80	..	2	..	1	1	..	..	..	..	..	..	..	0	4
4	10^{-3}	8 hr.	..	..	4	..	..	..	..	..	..	..	..	..	..	0	4
40	10^{-4}	—	0	0	40	..	..	..	..	..	..	..	..	..	..	0	40
15	10^{-4}	Immediately	125	7	..	..	1	..	..	..	..	2	2	..	5	5	10
4	10^{-4}	4 hr.	80	6	..	..	..	..	..	..	..	..	2	..	..	2	2
4	10^{-4}	8 hr.	72	6	..	1	..	..	1	..	..	..	..	..	..	2	2
4	10^{-4}	12 hr.	104	6	1	..	..	..	..	..	..	1	1	..	..	1	3
3	10^{-4}	16 hr.	80	6	..	1	..	..	..	..	..	1	..	..	..	1	2
4	10^{-4}	20 hr.	72	6	..	..	1	..	..	..	..	1	1	..	..	1	3
10	10^{-5}	—	0	0	7	1	1	1	..	..	..	..	..	..	..	0	10
12	10^{-5}	Immediately	112	7	..	..	..	1	..	..	..	1	3	1	1	5	7
9	10^{-5}	Immediately	80	6	..	..	..	..	..	..	..	1	3	..	..	5	4
6	10^{-5}	4 hr.	32	1	..	..	..	..	1	1	..	..	..	..	..	3	3
6	10^{-5}	8 hr.	40	1	..	..	..	..	1	.	..	2	..	..	..	3	3
3	10^{-6}	—	0	0	..	..	..	1	1	1	..	..	..	..	..	0	3
3	....	.....	...	..	1	..	..	..	..	..	..	..	2	..	..	0	3

We next turned our attention to the study of the effect of injecting sulfanilamide into animals which had been infected with varying numbers of organisms. The treatment was begun immediately or five or eight hours after infection. The results are recorded in table 4.

When 1 cc. of a 10^{-3} dilution of a sixteen hour broth culture of the organisms was injected intraperitoneally into mice and treatment begun immediately by injecting 1 cc. of an 0.8 per cent solution of sulfanilamide every six hours for four doses and then 1 cc. every day, it was found that all the animals except 1 survived during the period of treatment. When the treatment was stopped, most of the animals died. When treatment was delayed four or eight hours, death occurred with regularity.

When dilutions of 10^{-4} were used and treatment was started immediately or within four hours, most of the mice could be saved as long as treatment was continued. The same results were obtained when fewer organisms were used.

In brief, then, it can be said that sulfanilamide prevents the death of mice against 100 to 1,000 lethal doses of hemolytic streptococci as long as the use of the drug is continued. When it is stopped the fatality rate is high. This indicates that the drug is not bactericidal for the organisms in the mouse but delays their growth so that death does not occur as long as it is administered. It is possible, of course, that the reason these organisms grow so freely once the drug is discontinued is the lack of specific antibodies in these animals. That is to say, mice are unable to produce antibacterial antibodies, and since the effect of the drug is no longer operative, the infection progresses and kills the animal.

COMMENT

In summing up, then, it can be said that sulfanilamide has a definite effect on the growth of hemolytic streptococci in vitro and in vivo. This is suggested by inhibitory and even bactericidal effects. While these effects are only slight in some cases, nevertheless they are probably of great importance for the final destruction of the bacteria by the defense mechanisms of the body. These conclusions are supported by in vitro as well as in vivo experiments.

From the experimental as well as the clinical evidence so far we are forced to conclude that at least two conditions are essential for the optimum therapeutic action of sulfanilamide: The chemical must be present in sufficient concentration to produce optimum bacteriostasis, and the body's defense mechanism must acquire or retain the power to destroy viable organisms. From our own experiments there is evidence that a concentration of at least 7 to 10 mg. per hundred cubic centimeters is necessary for maximal bacteriostasis and that specific antibody and active phagocytosis are necessary for destruction. In experimental animals mice and rabbits, the body is rid of organisms by means of phagocytosis, and the role of specific antibody is less certain.

It is perhaps not wholly justifiable to explain what happens in man on a basis of results in vitro and in animal experiments. It has been

pointed out by Holman and Duff [18] that in experimental studies the most virulent strains of bacteria are used and the most sensitive animals are chosen. There is no such preliminary contact between organism and tissues as is present in the stage of invasion, and defenses must, of necessity, be mobilized rapidly if they are to be effective. The same authors said that there is good evidence that sulfanilamide is most effective in the progressive stages of an infection in which active and continuous tissue reactions are taking place and that the bacteriostatic effect of the drug often tips the balance in favor of a cure.

In other words, there are good reasons for believing that recovery from a hemolytic streptococcic infection depends on the mobilization of the body's defenses so that the effects of the bacteria can be neutralized. Once the defense mechanism gains the upper hand, a definite cure takes place. If, on the other hand, the bacteria multiply rapidly, injure tissues, invade the body with rapidity and overwhelm it before the defenses can be mobilized or increased, then the balance will be tipped the other way. For the present, at least, it seems safe to say that sulfanilamide slows the growth of the organisms and in this way allows the defense mechanism of the tissue to mobilize in an effective manner.

There are many problems to be studied and worked out, especially the action of sulfanilamide on the defensive mechanisms of the body. Until such information is available it is well not to draw any rigid conclusions concerning the full mechanism by which this drug exerts its effects.

SUMMARY AND CONCLUSIONS

From a study of the mode of action of sulfanilamide in vitro and in vivo, the following facts emerged:

1. When sulfanilamide was added to whole defibrinated blood so that the concentration was 7 mg. or more per hundred cubic centimeters, there was definite bacteriostasis, and in some instances a definite bactericidal effect was demonstrated.

2. We were unable to demonstrate a bactericidal effect of sulfanilamide when it was added to plasma, although bacteriostasis was present in plasma containing sulfanilamide. This bacteriostasis was less striking in plasma than it was in whole blood.

3. The samples of blood which showed a bactericidal effect with sulfanilamide were those containing some natural antibodies. It is suggested, therefore, that sulfanilamide may enhance the bactericidal effect of whole blood provided natural antibodies are present.

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18. Holman, W. L., and Duff, G. L.: Sulphanilamide and Similar Compounds in Chemotherapy, Am. J. M. Sc. **195**:378, 1938.

4. In the cases in which it was not possible to demonstrate a bactericidal effect, a bacteriostatic effect was shown. When the number of organisms was small there was almost complete bacteriostasis; when the inoculum was larger the rate of multiplication was slower, and the number of organisms at the end of twenty-four hours was less than in the controls.

5. It appears that antibodies are important in destroying hemolytic streptococci in vitro even in the presence of sulfanilamide.

6. The principal action of sulfanilamide in vitro is to slow the growth of the organism. It has no direct bactericidal effect on any serologic type of hemolytic streptococci.

Miss Marjorie L. Jewell and Miss Eleanor M. Fleming rendered technical assistance.

COMPARATIVE EFFECTS ON EARLY SYPHILIS OF COMBINED AND OF ALTERNATING TREATMENT

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AND
CHARLES W. BARNETT, M.D.
SAN FRANCISCO

Continuous treatment is generally acknowledged to be superior to the intermittent type in the treatment of early syphilis. The simplest and most commonly used form of continuous therapy consists of courses of an arsphenamine alternating with courses of a heavy metal. Various forms of combined treatment, in which the two types of drugs have been given at the same time through at least part of the treatment, also have been widely used. In most of these modifications, the period of simultaneous administration has been comparatively short, or treatment was given intermittently rather than continuously. Stokes [1] more recently has used a "simultaneous (concurrent) continuous" form of therapy in which the individual courses are much longer than the intervals between courses. The results of this particular form of treatment have not been reported as yet.

In the last ten years in the syphilis clinic of the Stanford University School of Medicine, two plans of treatment have been used for early syphilis. Formerly, treatment was carried out with alternating courses of neoarsphenamine and iodobismitol [2] but more recently a system of combined therapy resembling the simultaneous method described by Stokes has been used. The purpose of this paper is to compare the clinical and serologic results obtained by these two methods of therapy.

In the alternating type of treatment, courses of ten weekly injections of neoarsphenamine were alternated with courses of twenty weekly injections of iodobismitol, except for the fact that for the first ten weeks the two drugs were given simultaneously. The usual dose of

From the Division of Dermatology and Syphilology, Stanford University School of Medicine.

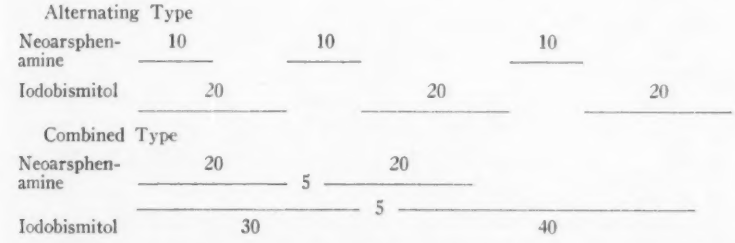
1. Stokes, J. H.: Modern Clinical Syphilology: Diagnosis, Treatment, Case Studies, Philadelphia, W. B. Saunders Company, 1934, p. 767.

2. The term iodobismitol as used in this report refers to iodobismitol and to iodobismitol with saligenin. The former was used in the majority of the cases, but in the last two years of the study only the latter was available.

neoarsphenamine was 0.6 Gm. for men and 0.45 Gm. for women. The dose of iodobismitol was 2 cc. In a few cases one or more courses of mapharsen were substituted for courses of neoarsphenamine, and occasionally the initial course of neoarsphenamine was given without iodobismitol. In some cases sobisminol was used in place of iodobismitol; there were others in which the patients were given a course of mercuric salicylate late in the course of treatment, but never before at least two courses of bismuth had been administered.

In the combined type of treatment, neoarsphenamine and iodobismitol were given simultaneously once every week for a twenty week period. Neoarsphenamine was then omitted for five weeks, after which a second course of twenty injections was given. The initial course of iodobismitol was continued until it equaled thirty doses, and a second course, of forty doses, was given after an interval of five weeks. The usual dose of neoarsphenamine was 0.45 Gm. for both men and women, and the dose of iodobismitol was 2 cc. The variations in the drugs which were used were similar to those on the alternating type except that in no instance was mercury included.

A diagram of the two types of treatment follows. The lines indicate courses of weekly injections, and the figures, the number of weeks of treatment.



The material studied consisted of 236 cases of primary or secondary syphilis in which the alternating type of treatment was given and of 81 similar cases in which the patients received the combined type. No patients were included who had not received at least twenty injections within a period of not less than five months.

There are a number of ways by which the effectiveness of the treatment of early syphilis may be evaluated. The most important of these are the serologic response, the incidence of involvement of the nervous system and the incidence of serologic or clinical relapse. We have appraised our results on the basis of these criteria.

The serologic results obtained by the two types of treatment at the end of five and of eighteen months are compared in table 1.

Of the patients whose treatment was started in the seronegative primary stage, all but 1 continued to present a seronegative reaction. No significance can be attached to a single relapse. Of the patients whose condition was initially seropositive, a higher percentage of reversals in the Wassermann reaction was observed at five months among those receiving the combined type of treatment. The same difference, although less marked, was observed at eighteen months.

An examination of the cerebrospinal fluid was carried out at some time after the first six months of treatment for every patient who did

TABLE 1.—*Serologic Results Five Months and Eighteen Months After the Beginning of the Alternating and of the Combined Type of Treatment*

	Type of Treatment	
	Alternating	Combined
Seronegative primary syphilis		
Total number of patients	34	14
Seronegative reactions at 5 mo.	34	14
Patients examined serologically at 18 mo.	20	5
Seronegative reactions at 18 mo.	20	4
Seropositive primary and secondary syphilis		
Total number of patients	202	67
Patients examined serologically at 5 mo.	180	58
Seronegative reactions at 5 mo.	111 (62%)	46 (79%)
Seropositive reactions at 5 mo.	69 (38%)	12 (21%)
Patients examined serologically at 18 mo.	114	25
Seronegative reactions at 18 mo.	96 (84%)	23 (92%)
Seropositive reactions at 18 mo.	18 (16%)	2 (8%)

TABLE 2.—*Incidence of Positive Serologic Reactions of the Cerebrospinal Fluid with the Alternating and with the Combined Type of Treatment*

	Type of Treatment	
	Alternating	Combined
No. of cerebrospinal fluids examined	150	43
No. with positive reactions	24	7
Percentage of positive reactions	16%	16%

not refuse to undergo spinal puncture. The results, given in table 2, show the same incidence of involvement of the nervous system with the two types of treatment.

Although the incidence of involvement of the nervous system is not affected by the type of treatment, the combined form shows a slight advantage over the alternating in effecting serologic reversal. This is of minor importance, since the final criterion of therapeutic efficiency is the clinical outcome, which is not dependent on reversal of the Wassermann reaction. A much more valuable indication of the effectiveness of therapy is the frequency of clinical or serologic relapse. The incidence of relapse observed with the two types of treatment in our series

is shown in table 3. The relapses have been divided into two types, those in which only the serologic reactions became positive and clinical relapses. All the clinical relapses were of the mucocutaneous type, and all were accompanied by recurrence of the positive Wassermann reaction.

This table indicates that the combined type of treatment is inferior to the alternating type in the prevention of relapse, but the significance of this difference is modified by the consideration of several factors. The most important of these are the regularity of treatment, the amounts of antisyphilitic drugs given and the total period of observation.

Therapy was considered to be regular when more than 80 per cent of the appointments for treatment were kept and irregular when the attendance was less than 80 per cent. This measure of regularity does

TABLE 3.—*Incidence of Relapse with the Alternating and with the Combined Types of Treatment*

	Type of Treatment	
	Alternating	Combined
Total number of cases	236	81
Total number of relapses	18 (7.6%)	10 (12.3%)
Number of serologic relapses	15 (6.3%)	6 (7.4%)
Number of mucocutaneous relapses	3 (1.3%)	4 (4.9%)

TABLE 4.—*Incidence of Relapse in Relation to the Regularity of Treatment*

	Type of Treatment	
	Alternating	Combined
Relapses with regular treatment	6	8
Relapses with irregular treatment	12	2

not distinguish prolonged irregular treatment from more or less regular treatment interspersed with periods of complete lapse. The incidence of relapse in relation to the regularity of treatment with the two types of therapy is shown in table 4.

Since the majority of relapses with the alternating type of therapy occurred in the patients receiving irregular treatment, it seems that this irregularity must have contributed to their production. On the other hand, most of the relapses with the combined type occurred in patients receiving regular treatment, indicating that the type of treatment itself was probably at fault. This difference is of even greater significance than is indicated in the table because the average regularity of attendance of all patients in the group with alternating treatment was greater than that in the group with combined treatment, being 88 per cent and 83 per cent, respectively.

In table 5 the total amount and the number of doses of neoarsphenamine and of iodobismitol given in the alternating and of those given in the combined type of therapy are shown. In the few cases in which mapharsen or sobisminol was substituted for a part of the treatment, a conversion was made to equivalent doses of neoarsphenamine and iodobismitol in preparing the table.

The patients who received the alternating type of therapy were given slightly more bismuth but considerably less neoarsphenamine than those who received the combined type. This occurred in spite of the fact that the average duration of therapy was only sixteen months for the combined type, as compared with nineteen months for the alternating type.

In the treatment of early syphilis, the drug of primary importance is generally considered to be arsphenamine or one of its derivatives. One

TABLE 5.—*Total Amounts and Number of Doses of Neoarsphenamine and of Iodobismitol Given in the Alternating and in the Combined Type of Treatment*

	Type of Treatment	
	Alternating	Combined
Neoarsphenamine		
Average number of doses	29	37
Average total dose in Gm.	15	18
Iodobismitol		
Average number of doses	49	45
Average total dose in Gm.	5.8	5.5

would therefore expect that patients receiving larger amounts of these preparations would show better clinical results. This expectation is not fulfilled in our series, since the group given combined therapy, which showed a higher incidence of relapse than that given alternating therapy, received a larger average total amount of neoarsphenamine. The slight difference between the amount of bismuth given and the average duration of therapy in the two groups is too small to be of much significance and is probably explained by the fact that a number of patients in the series receiving combined therapy were still under treatment at the time this study was made.

The most important difference between the two groups, aside from the method of treatment, is in the average total period of observation, which was twenty-eight months for the series receiving alternating therapy and only eighteen months for that receiving combined therapy. The average time of relapse in the group given alternating therapy was twenty-three months after the beginning of treatment. Since the group given combined therapy was observed for only eighteen months, additional relapses would be expected to occur. In fact, several such

relapses have been observed since this study was terminated. It is therefore of particular significance that the group given combined treatment showed a higher incidence of relapses in spite of a much shorter period of observation.

Since the inferior results of the combined type of therapy appear more obvious when regularity of treatment, total dosage of drugs and duration of observation are considered, another explanation for this difference in therapeutic effect must be sought. Experimental evidence reported by various observers [3] indicates that prolonged use of any therapeutic agent, particularly in small doses, may lead to drug fastness. This evidence suggests that the long courses, separated by only short intervals, used in the combined type of treatment may be the cause of its inferiority.

SUMMARY AND CONCLUSIONS

1. The results of treatment in a series of 81 patients with early syphilis given combined neoarsphenamine and bismuth therapy are compared with the results in a similar series of 236 patients receiving an alternating type of treatment.

2. The frequency of serologic reversal at the end of five and of eighteen months of treatment was slightly greater for the patients given combined treatment than for those given the alternating type. This fact is of minor importance, since the rate of serologic reversal is not a satisfactory index of therapeutic efficiency.

3. The incidence of abnormal cerebrospinal fluids was the same in the two series.

4. The incidence of relapse, both clinical and serologic, was greater among the patients given combined treatment than among those given the alternating type. When the factors of regularity of treatment, total dosage of the drugs and duration of observation are taken into consideration, this difference assumes an added significance. Since the prevention of relapse is the most important indication of efficiency of treatment, the inferiority of the combined type of therapy in this respect is sufficient to make further use of this type of treatment undesirable.

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3. Akatsu, S., and Noguchi, H.: The Drug Fastness of Spirochetes to Arsenic, Mercurial and Iodide Compounds in Vitro, J. Exper. Med. **25**:349, 1917. Brown, W., and Pearce, L., cited by Stokes.[1] Feldt, A.: Ueber Arzneifestigung von Spirochäten im Tierversuche, Klin. Wchnschr. **11**:1378, 1932. Krantz, W.: Untersuchungen über die Wirkungen ungenügender Salvarsanmengen bei experimenteller Kaninchensyphilis, München. med. Wchnschr. **80**:2040, 1933.

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1938

ASHTON GRAYBIEL, M.D.
WITH THE EDITORIAL ASSISTANCE OF
PAUL D. WHITE, M.D.
BOSTON

All students of heart disease will welcome the appearance of the *British Heart Journal,* which is being published at the request of the Cardiac Society of Great Britain and Ireland. There, it will fill a need which has been long felt and hitherto neglected. Being addressed chiefly to practicing physicians and cardiologists, it must not be regarded as merely a successor to *Heart,* which was restricted in scope. This journal will soon command a leading position in the field if it follows the precept expressed by Sir Thomas Lewis in the foreword as follows:

> The success of the new journal will depend upon the quality and not primarily upon the quantity of the matter which it publishes. Originality of observation and of view will be the touchstone of quality. The work of editing is uncreative; an editor can publish only what is offered; he will use most of what is offered. The journal's success is governed, therefore, from the source of the material. The best contributors will submit for publication only sound and original matter and thought. They will edit their own work; will judge their own text impartially and will prune it ruthlessly, thinking of the standard of work accomplished and to be reported and not of personal interest; they will prepare their manuscript in all particulars to save further labour; they will facilitate the reading by every device of conciseness, of simplicity, of clarity, and of accuracy, in composing text, figure explanation, and reference; for every hour so spent by one who writes will save countless hours by the many who afterward read. They will remember that the work of editing is a gratuitous and unenviable task, and they will bow loyally to editorial decision.

ELECTROCARDIOGRAPHY

Asher and Hoecker[1] have described a device which, when attached to an electrocardiograph, permits immediate and continuous viewing of the electrocardiogram. This device consists essentially of a moving

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1. Asher, G., and Hoecker, F.: The Lag-Screen Belt Electrocardiogram, Am. Heart J. **16**:51, 1938.

endless belt coated with material which phosphoresces when exposed to the light beam of the electrocardiograph. The degree of phosphorescence is sufficient to define the wave form so that it appears much as it does in the electrocardiogram (only the finest details are lost), thus permitting adequate inspection of the complexes of a considerable strip of successive beats. The many advantages of this apparatus for clinical and teaching use are readily apparent.

Wilson and Johnston [2] have reviewed the history of the development of the vectorcardiogram and have described their own recording apparatus. A vector is a line, or a quantity that may be represented by a line, conceived to have both a fixed length and a direction in space but no fixed position. Consequently, since the resultant electromotive force produced by the heart at a given instant has both magnitude and direction, it may be represented by a vector drawn with the center of Einthoven's triangle as its origin. When the excitatory process in the heart is advancing or retreating, the size and direction of this vector vary from instant to instant so that its terminus describes a continuous curve. The relations between the vectorcardiogram and the three leads of the standard electrocardiogram have been clearly described by the authors and many examples of different types of curves shown. Conclusions as to the ultimate usefulness of the vectorcardiogram have been avoided, but some of its possibilities have been pointed out.

Sigler [3] has observed definite changes in the appearance of the QRS and T waves in the electrocardiogram following alterations from the recumbent to the sitting or standing position. The change may occur in the T wave alone, the amplitude diminishing or T becoming inverted in lead III or in leads II and III. The changes in the QRS complex consist chiefly in shifts of the electrical axis. The author has discussed certain theoretic implications and has concluded that the changes observed do not conform to the theory of the Einthoven equilateral triangle, because the shift in the electrical axis is not always the same as that predicted from the supposed shift of the anatomic axis. The preferred explanation is that on alteration of body posture there occurs a change in contact of the adjacent conducting mediums with different portions of the heart, thereby producing variations in conduction. As the author has stated, it is truly important to know the posture of the subject when the tracing was taken before attaching pathologic significance to certain apparent abnormalities.

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2. Wilson, F. N., and Johnston, F. D.: The Vectorcardiogram, Am. Heart J. **16**:14, 1938.

3. Sigler, L. H.: Electrocardiographic Changes Occurring with Alterations of Posture from Recumbent to Standing Positions, Am. Heart J. **15**:146, 1938

Several authors [4] have described the electrocardiographic findings following the administration of various drugs and following nerve stimulation. Of particular interest is the report by Chamberlain, who found that resection of the cervical sympathic ganglions has no effect on the form of the electrocardiogram. He also found that stimulation of the left sympathetic ganglion produces no constant changes but that stimulation of the one on the right may decrease the amplitude of R or increase T or both. The changes lasted only for a few minutes after the stimulation ceased.

Hill,[5] while trying various chest leads, found that whenever three leads were taken in the usual order from any three points, the sum of the first and third was always equal to the second. He then charted the potential distribution on the surface of the chest throughout the cardiac cycle, which suggested that the current to which the electrocardiogram is due runs around the thoracic wall and not through the chest, as hitherto commonly assumed. This is simply another piece of evidence which, when added to the rest, seems to indicate that the theory of the equilateral triangle and the meaning of the term axis deviation will need modification.

ROENTGENOLOGY

Robb and Steinberg [6] have described a practicable procedure which has enabled them successfully to visualize the chambers of the heart

4. Chamberlain, E. N.: The Results of Sympathetic Stimulation and Extirpation on the Human Electrocardiogram, Clin. Sc. **3**:267, 1938. Winkler, A. W.; Hoff, H. E., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, Am. J. Physiol. **124**:478, 1938. Volpitto, P. P., and Marangoni, B. A.: Electrocardiographic Studies During Anesthesia with Intravenous Barbiturates, J. Lab. & Clin. Med. **23**:575, 1938. Dameshek, W.; Loman, J., and Myerson, A.: Human Autonomic Pharmacology: VII. The Effect on the Normal Cardiovascular System of Acetyl-Beta-Methylcholine Chloride, Atropine, Prostigmin, Benzedrine, with Especial Reference to the Electrocardiogram, Am. J. M. Sc. **195**:88, 1938. Stewart, H. J., and Watson, R. F.: The Effect of Digitalis on the Form of the Human Electrocardiogram, with Special Reference to Changes Occurring in the Chest Lead, Am. Heart J. **15**:604, 1938. Hafkesbring, R., and MacCalmont, W.: The Effect of Sodium Amytal, Sodium Barbital and Nembutal on the Electrocardiogram, J. Pharmacol. & Exper. Therap. **64**:43, 1938. Miller, J. R., and Van Dellen, T. R.: Electrocardiographic Changes Following the Intravenous Administration of Magnesium Sulfate, J. Lab. & Clin. Med. **23**:914, 1938. Stearns, W. H.; Drinker, C. K., and Shaughnessy, T. J.: Electrocardiographic Changes Found in Twenty-Two Cases of Carbon Monoxide (Illuminating Gas) Poisoning, Am. Heart J. **15**:434, 1938.

5. Hill, A.: Analysis of the Normal QRS Deflection, Lancet **2**:1110, 1938.

6. Robb, G. P., and Steinberg, I.: Practical Method of Visualization of Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Man, J. Clin. Investigation **17**:507, 1938; Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Vessels in Man: A Practical Method, Am. J. Roentgenol. **41**:1, 1939.

and the great vessels in the thorax. The method consists of the rapid injection of 25 to 45 cc. of a 70 per cent solution of diodrast into a vein in the arm and the obtaining of roentgenograms when the chambers of the heart and the blood vessels are filled with the material that is opaque to the roentgen ray. Diodrast was found to have usually only mild pharmacologic effects when injected; only occasionally were severe reactions observed. This method will aid in the recognition of abnormalities of the mediastinal and hilar blood vessels and in the differentiation of these vessels from adjacent structures, such as mediastinal neoplasms. Visualization of the cardiac chambers, the ventricular walls, the interventricular septum and the valves will provide information about the normal and the diseased heart heretofore unobtainable. The authors have emphasized the fact that the method promises to be of practical value in the differential diagnosis of heart disease.

CARDIAC ARRHYTHMIAS

Stewart and his co-workers[7] made observations on the effect of abnormal rhythms on the circulation. They found that auricular fibrillation, auricular flutter, paroxysmal auricular and paroxysmal ventricular tachycardia in patients without congestive failure are associated with decrease in the cardiac output per minute and per beat, decrease in velocity of blood flow, dilatation of the heart and decrease in the work of the heart per beat. As a consequence these patients fall in the heart failure zone when the abnormal rhythm is present. On the other hand, in instances of heart block, sinus bradycardia and coupled rhythm, although the cardiac output per minute is decreased, the output per beat is increased, and the work per beat is commensurate with the size of the heart. Thus, the rapid abnormal cardiac rhythms are associated with marked decrease in the functional capacity of the heart, while the slow abnormal rhythms are not incompatible with a normal circulatory function when the subject is at rest.

Abnormally Short PR Interval.—Clerc and his associates[8] have described instances of shortening of the PR interval in the electrocardiogram which was not associated with anomalies of the QRS complex. This stands in contrast to the short PR interval associated with

7. Stewart, H. J.; Deitrick, J. E.; Crane, N. F., and Thompson, W. P.: Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms: Observations Relating to Rhythms Associated with Rapid Ventricular Rate and to Rhythms Associated with Slow Ventricular Rate, J. Clin. Investigation **17**:449, 1938.

8. Clerc, A.; Levy, R., and Cristesco, C.: A propos du raccourcissement permanent de l'espace P-R de l'électrocardiogramme sans déformation du complexe ventriculaire, Arch. d. mal. du cœur **31**:569, 1938.

prolongation of QRS, which has been recognized for years. Certain clinical affinities exist between the two types, namely, their appearance in young persons with irritable but otherwise normal hearts and the benignity of the prognosis.

Bundle Branch Block.—Yater [9] has written a comprehensive and critical treatise on the pathogenesis of bundle branch block. The important literature on this subject has been reviewed, including anatomic, physiologic, histopathologic and clinical studies. Especial emphasis has been given to his own pathologic studies in 16 cases and to 6 cases studied by means of serial sections through the conduction system. He found that bundle branch block is due usually to coronary atherosclerosis and less commonly to rheumatic involvement or to hypertension resulting in strain of the left ventricle and impairment of the nutrition of the endocardium and bundle branch. His studies showed that bundle branch block is usually associated with bilateral bundle branch lesions, although one branch is usually more seriously affected than the other and probably determines the essential form of the curve. The adjective right or left when applied to bundle branch block merely indicates the branch more seriously affected. He concluded that any increase of the QRS interval beyond 0.1 second may indicate lesions of the bundle branches and that a bundle branch need not be entirely destroyed at any level in order to produce the characteristic electrocardiographic changes.

Paroxysmal Bundle Branch Block.—Comeau, Hamilton and White [10] have presented in detail 13 cases of paroxysmal bundle branch block and have added to their analysis 58 cases previously reported. They have pointed out that this arrhythmia is associated with serious organic heart disease and should be sharply differentiated from bundle branch block with a short PR interval, which is of no serious significance. Paroxysmal bundle branch block (without a very short PR interval) is most often due to coronary sclerosis but in some instances is associated with rheumatic heart disease, diphtheria and factors that cannot clinically be ascertained. Although physiologic changes may act as precipitating factors, they are effective only in the presence of actual changes in the conducting tissue. The authors believe that the prognosis is similar to that in permanent bundle branch block and depends upon the type and severity of the associated heart disease.

9. Yater, W. M.: Pathogenesis of Bundle Branch Block: Review of the Literature; Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction System, Arch. Int. Med. **62**:1 (July) 1938.

10. Comeau, W. J.; Hamilton, J. G. M., and White, P. D.: Paroxysmal Bundle-Branch Block Associated with Heart Disease, Am. Heart J. **15**:276, 1938.

Treatment of Cardiac Arrhythmias.—Fahr [11] has summarized the present status of the treatment of common cardiac irregularities. New material has not been presented, but his paper may be read with profit by all those desiring information on this subject.

CONGENITAL HEART DISEASE

In addition to the articles herewith reviewed, the interested reader may refer to other reports,[12] which can be mentioned here only by title.

Patten [13] has written an excellent paper describing the various types of developmental defects encountered at the foramen ovale. He has begun with a summary of the normal prenatal and postnatal development of the interatrial septums, an understanding of which is necessary for the appreciation of what follows. In the separation of the primitive common atrium into right and left chambers, two septums are directly involved, which are termed septum primum and septum secundum on the basis of their sequential appearance. The septum primum, starting as a crescentic ridge on the dorsocephalic part of the atrial wall, grows toward the artrioventricular canal. About the time it seems as if the septum primum would shut off the left atrium from the right, a secondary opening develops near its origin from the dorsocephalic wall. The appearance of this second ostium is of fundamental functional significance, as it allows balanced atrial intakes and prevents defective development of the left side of the heart. About this time the septum secundum begins to develop just to the right of the septum primum. It does not become a complete partition but leaves a characteristic oval aperture, which is the foramen ovale. The remaining portion of the septum primum lies as a loose flap over the foramen ovale and acts as a one way valve, permitting flow only from right to

11. Fahr, G.: The Treatment of Cardiac Irregularities, J. A. M. A. **111**:2268 (Dec. 17) 1938.

12. Manchester, B., and White, P. D.: Dextrocardia with Situs Inversus Complicated by Hypertensive and Coronary Heart Disease, Am. Heart J. **15**:493, 1938. Krumbhaar, E. B., and Ehrich, W. E.: Varieties of Single Coronary Artery in Man, Occurring as Isolated Cardiac Anomalies, Am. J. M. Sc. **196**:407, 1938. Lev, M., and Saphir, O.: Congenital Aneurysm of the Membranous Septum, Arch. Path. **25**:819 (June) 1938. Oppenheimer, E. H.: Partial Atresia of the Main Branches of the Pulmonary Artery Occurring in Infancy and Accompanied by Calcification of the Pulmonary Artery and Aorta, Bull. Johns Hopkins Hosp. **63**:261, 1938. Gibson, S., and Clifton, W. M.: Congenital Heart Disease: A Clinical and Postmortem Study of One Hundred and Five Cases, Am. J. Dis. Child. **55**:761 (April) 1938. Graybiel, A.; Strieder, J. W., and Boyer, N. H.: An Attempt to Obliterate the Patent Ductus Arteriosus in a Patient with Subacute Bacterial Endarteritis, Am. Heart J. **15**:621, 1938.

13. Patten, B. M.: Developmental Defects at the Foramen Ovale, Am. J. Path. **14**:135, 1938.

left. Following birth there is a gradual diminution of the interatrial communication, and at the end of a month the foramen ovale is functionally closed, although a probe may be freely passed. During the next six to eight months the flaplike valve is converted into a fixed septal structure, and later fibrous adhesion of the valvula to the septum occurs. In 20 to 25 per cent of adults the fibrous adhesion is never entirely completed. Such failures of complete adhesion appear to be of no functional significance and may be regarded as variations of the normal rather than as abnormalities, although in the event of disturbances in the pulmonary circuit an area of incomplete adhesion may again become a path for transseptal flow.

Patten believes that pathologic lesions rarely, if ever, appear to play a part in the primary causation of a developmental septal defect but that these defects are the result of "developmental arrests" and abnormalities in the normal process of resorption of tissue. The most common type of defect at the foramen ovale is that in which there has been just a little too much resorption of the septum primum, leading to failure of the valvula to overlap the foramen completely. Cases have been presented in which abnormal interatrial openings appeared as the result of:

(1) underdevelopment of septum secundum; (2) resorption of septum primum starting in the normal location but going too far; (3) resorption of septum primum taking place in abnormal locations; and (4) overgrowth of septum secundum.

The author has emphasized the necessity of discriminating more critically between an open foramen ovale with a competent but unfused valve and a frankly unguarded (patent) foramen ovale. In the former instance, leakage, if it occurs, is only from the right to the left, and crossed emboli are comparatively frequent. In the widely patent foramen ovale the conditions are much the same if there is associated pulmonary stenosis, because the transseptal flow is from right to left. But when pulmonary stenosis is absent the interatrial flow is from left to right and may produce a well recognized clinical picture. In contrast with certain other types of congenital defects, subacute bacterial endocarditis is strikingly absent, and chronic pericardial disease, crossed embolism and pulmonary tuberculosis are noticeably rare concomitants.

Barclay and Franklin,[14] using direct roentgen cinematography combined with injection of colloidal thorium dioxide, found that the foramen ovale remained patent after functional closure of the ductus arteriosus

14. Barclay, A. E., and Franklin, K. J.: The Time of Functional Closure of the Foramen Ovale in the Lamb, J. Physiol. **94**:256, 1938.

in lambs delivered by cesarean section. The latest time at which evidence of such patency was obtained was six minutes and forty seconds after delivery.

Taussig and her co-workers [15] have reported 4 cases of interauricular septal defects and have discussed the clinical and pathologic data. The essential pathologic features are a widely patent foramen ovale, great dilatation and hypertrophy of the right auricle and the right ventricle, relative enlargement of the pulmonary artery and a small left ventricle and aorta. The significant findings on physical examination are deformity of the left side of the chest of a frail person, marked cardiac enlargement to the right and usually a harsh systolic murmur and thrill in the second and third left interspaces. Clubbing and cyanosis are absent. Common sequelae are cardiac arrhythmias, superimposed rheumatic infections, pulmonary infections, paradoxic emboli and freedom from subacute bacterial endocarditis.

Barclay and his associates,[16] in order to find out more definitely the time and manner of closure of the ductus arteriosus, succeeded in obtaining roentgenographic records of the ductus in full term lambs immediately after cesarean section. The injection of thorium dioxide was begun within thirty seconds after delivery, and serial records were taken at the rate of about one a second. It was found that the flow of blood through the ductus is sluggish as early as twenty-five seconds after delivery and that functional closure is complete within the first minute. Closure is not the result of a simple contraction of the walls of the ducts but of twisting and kinking of the lumen and is unrelated either to interruption of the maternal circulation or to the lamb's respiration.

Taussig,[17] in a classic paper, has described the clinical and pathologic features of complete transposition of the great vessels in 4 cases, emphasizing the clinical signs by which this anomaly can be recognized during life. She points out that the fundamental feature in these cases is the abnormal torsion of the aortic septum, whereby the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. In order that this malformation may be compatible with life, even for a short time, there must be an additional malformation which permits some crossing of the systemic and pulmonary circulations. The problem resolves itself into the recognition of the transposition and an

15. Taussig, H. B.; Harvey, A. M., and Follis, R. H., Jr.: The Clinical and Pathological Findings in Interauricular Septal Defects: A Report of Four Cases, Bull. Johns Hopkins Hosp. **63**:61, 1938.

16. Barclay, A. E.; Barcroft, J.; Barron, D. H., and Franklin, K. J.: X-Ray Studies of the Closing of the Ductus Arteriosus, Brit. J. Radiol. **11**:570, 1938.

17. Taussig, H. B.: Complete Transposition of the Great Vessels, Am. Heart J. **16**:728, 1938.

analysis of the concomitant malformations. In regard to the former, Taussig found that the diagnosis is based primarily on the changes in the shadow cast by the great vessels, combined with persistent cyanosis. In the anteroposterior view of the heart the shadow cast by the great vessels is narrow because the pulmonary artery lies directly behind the aorta; in the left anterior oblique view the two vessels lie parallel, and the shadow cast by these vessels is abnormally wide. The shape of the heart is also suggestive, especially enlargement of the right ventricle and absence of the shadow cast by the pulmonary conus. The electrocardiogram may or may not be of aid in the recognition of right ventricular enlargement.

RHEUMATIC HEART DISEASE

Etiology.—During the past few years some evidence has been presented suggesting the possibility that rheumatic fever is due to a virus infection. This work, which has been summarized in previous reviews, revealed that suspensions of particles bearing a close resemblance to elementary bodies of known virus infection can be prepared from exudates from patients with acute rheumatic fever, rheumatoid arthritis and chorea. These particles were found to be agglutinated by serum from patients suffering from the corresponding disease, whereas various control suspensions were not agglutinated. Although these observations were not confirmed by all workers, it was only reasonable that the infectivity of these virus-like bodies should be tested.

Eagles and his co-workers [18] have made such tests by preparing suspensions of virus-like bodies from a variety of materials from rheumatic patients and testing them for infectivity in monkeys, both alone and in combination with streptococcus toxin and streptococci. As a result of the inoculations in certain instances the clinical behavior suggested possible cardiac damage, but this was not supported by the pathologic data. The authors, while recognizing the limitations of their study, concluded that no evidence has been obtained that the suspensions of the virus-like bodies possess infectivity.

Pathologic Features.—The pulmonary changes in acute rheumatic fever and in chronic rheumatic heart disease [19] are becoming better

18. Eagles, G. H.; Evans, P. R.; Keith, J. D., and Fisher, A. G. T.: Infection Experiments with Virus-Like Bodies from Rheumatism, J. Path. & Bact. **46**:481, 1938.

19. Gouley, B. A.: The Role of Mitral Stenosis and of Post-Rheumatic Pulmonary Fibrosis in the Evolution of Chronic Rheumatic Heart Disease, Am. J. M. Sc. **196**:11, 1938; The Evolution of the Parenchymal Lung Lesions in Rheumatic Fever and Their Relationship to Mitral Stenosis and Passive Congestion, ibid. **196**:1, 1938. Melnick, P. J.: Pulmonary Changes in Rheumatic Fever, Illinois M. J. **73**:336, 1938. Hadfield, G.: The Rheumatic Lung, Lancet **2**:710, 1938.

understood, and their clinical significance is being better appreciated. Of particular interest are Gouley's observations that in some patients with mitral stenosis the essential cause of heart failure is not valvular obstruction but rather an important and independent structural change in the lung. He believes that this phenomenon is in the beginning a direct result of rheumatic fever, the pneumonitis leading often to widespread fine interstitial fibrosis which may, after inflammatory recurrences, become progressively more severe. This he believes may play an important role in the causation of heart failure.

Clinical Features.—There has never been general agreement among clinicians regarding the value of tonsillectomy in cases of rheumatic heart disease, and recent reports [20] have not brought agreement any nearer. However, the evidence does indicate that tonsillectomy should not ordinarily be attempted during the acute or the subacute phase of rheumatic infection and that tonsillectomy does not prevent the recurrences of rheumatic manifestations. It does indicate that tonsillectomy in the case of a rheumatic patient who does not have cardiac involvement at the time of operation should be recommended, since it may aid in the prevention of rheumatic heart disease.

Taussig and Hecht [21] have reported 37 cases in which hypertension occurred in close association with an acute rheumatic episode in childhood. Demonstrable renal damage was not associated with the hypertension in any of these cases. Various possibilities are discussed, but the exact relation between the hypertension and the rheumatic infection is not clear. Salvesen's [22] account of 6 cases of "rheumatic nephritis" is interesting in this connection. These 6 cases were found among 287 cases of nephritis, and, in addition, a survey of 212 cases of rheumatic fever revealed acute nephritis to be present in 10 instances. Whether this represents more than a chance association is unknown. It is pointed out that infection of the upper respiratory tract sometimes precedes glomerulonephritis, just as it commonly precedes rheumatic fever.

20. Allan, W. B., and Baylor, J. W.: The Influence of Tonsillectomy upon the Course of Rheumatic Fever and Rheumatic Heart Disease: Study of One Hundred and Eight Cases, Bull. Johns Hopkins Hosp. **63**:111, 1938. Ash, A.: Influence of Tonsillectomy on Rheumatic Infection, Am. J. Dis. Child. **55**:63 (Jan.) 1938. Turnley, W. H.: Tonsillectomy for Rheumatism: Study of 3,172 Cases, Ann. Otol., Rhin. & Laryng. **46**:1050, 1938.

21. Taussig, H. B., and Hecht, M. S.: Studies Concerning Hypertension in Childhood: II. The Occurrence of Hypertension in Acute Rheumatic Fever in Childhood, Bull. Johns Hopkins Hosp. **62**:491, 1938.

22. Salvesen, H. A.: Rheumatic Fever and Nephritis, Acta med. Scandinav. **96**:304, 1938.

Keil [23] has written a comprehensive monograph on rheumatic subcutaneous nodules. He believes this term should be applied only to lesions occurring in the course of undoubted rheumatic fever. Pathologically, these nodules present certain well recognized characteristics, but these characteristics are not pathognomonic. They consist essentially of small unit areas, grossly visible to the naked eye as millet-sized bodies and microscopically divisible into an inner necrobiotic core, a middle cellular layer and a peripheral zone showing increased vascularity. He has arbitrarily separated the discussion of the rheumatic nodules seen in children and those seen in adults. In adults there is a tendency for these lesions to show atypical localization, their incidence is small and their diagnostic value is impaired because of the opportunities for confusing them with other lesions. In children the rheumatic nodule is considered by Keil to be highly specific of rheumatic fever, and evidence has been given by him that the heart is "practically" always affected concurrently in one form or another. The typical nodule in rheumatoid arthritis is thought to differ from that in rheumatic fever in many clinical attributes and in some pathologic respects. In this connection McEwen,[24] using a supravital staining technic, found that the cells of rheumatoid arthritis nodules have essentially the same characteristics as those of rheumatic fever.

Keil [25] has presented a critical survey of rheumatic erythemas based on 53 examples discovered among 523 cases of rheumatic disease. These erythemas comprised several varieties, which have been classified as follows:

1. Simple papular form
2. Ringed forms:
   (*a*) Erythema marginatum rheumaticum
   (*b*) Flat annular erythema

Each group has been considered separately, and this includes a description of the erythema, with its clinical attributes and its relation to active rheumatic disease.

Bland and Jones [26] have analyzed the fatal course of rheumatic fever and its sequelae in 306 young patients. Rheumatic fever was directly

23. Keil, H.: The Rheumatic Subcutaneous Nodules and Simulating Lesions, Medicine **17**:262, 1938.

24. McEwen, C.: Cytologic Studies on Rheumatic Fever: III. A Comparison of Cells of Subcutaneous Nodules from Patients with Rheumatic Fever, Rheumatoid Arthritis and Syphilis, Arch. Path. **25**:303 (March) 1938.

25. Keil, H.: The Rheumatic Erythemas: A Critical Survey, Ann. Int. Med. **11**:2223, 1938.

26. Bland, E. F., and Jones, T. D.: Fatal Rheumatic Fever, Arch. Int. Med. **61**:161 (Feb.) 1938.

responsible for the fatality in 250 instances. It was found that the age of onset was not significant but that the early years after the onset of the disease often proved to be a critical period. In the majority the fatal illness usually extended over several months and represented an exacerbation of long-standing and clinically recognizable rheumatic fever. Aside from the general clinical picture, certain features were of particular interest. Arthritis was not present in any case, although variable arthralgia causing some discomfort was present in about half the group. Chorea was encountered in only 2 instances during the terminal illness. Carditis was present in every patient and was manifested clinically by marked cardiac enlargement, tachycardia, characteristic murmurs and ultimate failure of the congestive type. Evidence of involvement of the lung and liver was frequently observed.

Boone and Levine [27] have studied the prognosis for 225 young patients with "potential rheumatic heart disease" and "rheumatic mitral insufficiency" followed for an average of 9.6 years. Of the former, about 5 per cent subsequently had mitral stenosis, aortic insufficiency or both. Of those with "mitral insufficiency," about 42 per cent subsequently had mitral stenosis or aortic insufficiency, while 58 per cent remained unchanged.

Keith [28] has presented further evidence that prolongation of the auriculoventricular conduction time, which is the most characteristic abnormality in the electrocardiogram of patients suffering from rheumatic heart disease, is due to overstimulation of the vagus nerve. He found the average PR interval to be 0.138 second, with a range of 0.12 to 0.17 second, in 26 children without heart disease, which agrees closely with figures reported by other investigators. Serial electrocardiograms of 200 patients with various rheumatic manifestations showed that the average maximum PR interval was much greater than the normal average, although the highest averages were observed when carditis was present. After the administration of atropine to 11 rheumatic children with a PR interval of 0.19 second or over, the average reduction in conduction time was 0.048 second, which is much greater than the average reduction of 0.013 second observed in a control group. From this and other supporting evidence Keith has concluded that overstimulation of the vagus nerve is present in acute rheumatic fever and that it is probably the result of direct overactivity of the nerve endings in the heart.

27. Boone, J. A., and Levine, S. A.: The Prognosis in "Potential Rheumatic Heart Disease" and "Rheumatic Mitral Insufficiency," Am. J. M. Sc. **195**:764, 1938.

28. Keith, J. D.: Over-Stimulation of the Vagus Nerve in Rheumatic Fever, Quart. J. Med. **7**:29, 1938.

Treatment.—Because of the relation between infections due to beta hemolytic streptococci and rheumatic fever, it was logical to try the effect of sulfanilamide in both the prevention and the treatment of the rheumatic attack. There have been many verbal and a few written reports [29] of its use. A few conclusions may be tentatively drawn, although more time is needed before a final evaluation can be safely made. Not only does sulfanilamide apparently fail to have any beneficial effect on the course of rheumatic fever, but, as a result of its use, certain rheumatic features may become manifest. Furthermore, the toxic effects of the drug are especially marked in these patients. On the other hand, when sulfanilamide (15 to 20 grains [0.97 to 1.29 Gm.] daily) was given continuously during the course of two winters to 30 patients with a recent history of acute rheumatic fever, none had any illness in which the diagnosis of rheumatic fever was brought into question. Thus it appears that sulfanilamide is contraindicated in acute rheumatic fever but may have a place in prophylaxis.

ARTERIAL HYPERTENSION

Pathogenesis.—Studies on experimental hypertension [30] continue to represent the most important advances being made in the field of

29. Swift, H. F.; Moen, J. K., and Hirst, G. K.: The Action of Sulfanilamide in Rheumatic Fever, J. A. M. A. **110**:426 (Feb. 5) 1938. Massell, B. F., and Jones, T. D.: The Effect of Sulfanilamide on Rheumatic Fever and Chorea, New England J. Med. **218**:876, 1938. Thomas, C. B., and France, R.: A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, Bull. Johns Hopkins Hosp. **64**:67, 1939.

30. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia, in Harvey Lectures, 1937-1938, Baltimore, Williams and Wilkins Company, 1938, p. 237. Dicker, E.: Recherches expérimentales concernant le mécanisme de l'hypertension d'origine rénale chez le chien, Arch. internat. de méd. expér. **13**:27, 1938. Fasciolo, J. C.; Houssay, B. A., and Taquine, A. C.: The Blood Pressure Raising Secretion of the Ischaemic Kidney, J. Physiol. **94**:281, 1938. Williams, J. R., Jr.; Harrison, T. R., and Mason, M. F.: Observations on Two Different Pressor Substances Obtained from Extracts of Renal Tissue, Am. J. M. Sc. **195**: 339, 1938. Merrill, A.; Williams, J. R., Jr., and Harrison, T. R.: The Site of Action of the Renal Pressor Substance, ibid. **196**:18, 1938. Merrill, A.; Williams, R. H., and Harrison, T. R.: The Effects of a Pressor Substance Obtained from the Kidneys on the Renal Circulation of Rats and Dogs, ibid. **196**:240, 1938. Child, C. G.: Observations on the Pathological Changes Following Experimental Hypertension Produced by Constriction of the Renal Artery, J. Exper. Med. **67**: 521, 1938. Pickering, G. W., and Prinzmetal, M.: Some Observations on Renin, a Pressor Substance Contained in Normal Kidney, Together with a Method for Its Biological Assay, Clin. Sc. **3**:211, 1938. Boyd, J. D., and McCullagh, G. P.: Experimental Hypertension Following Carotico-Aortic Denervation in the Rabbit, Quart. J. Exper. Physiol. **27**:293, 1938. Levy, S. E., and Blalock, A.: Experimental Attempts to Prevent or Abolish Hypertension That Is Associated with

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cardiovascular disease. The literature on this subject has increased to such an extent that a detailed summary is no longer within the scope of this review.

The revival of interest in experimental hypertension is largely due to Goldblatt and his co-workers, who have shown that in the dog permanent hypertension may follow constriction of the renal arteries. There has followed an impressive series of experiments by many workers designed to interpret the exact nature of this phenomenon.

The association of hypertension with renal disease has long been known but has always been attributed to the diminution of the excretory power of the kidney which allowed the retention of substances normally eliminated. Recent studies have shown, however, that renal hypertension may be produced in dogs without significantly decreasing the renal function. In fact, procedures which allow retention of renal excretory products, such as removing most or all of the renal substance or anastomosing a ureter to an iliac vein, do not produce hypertension. Experimental hypertension may follow the constriction of the renal arteries but cannot be produced unless the kidneys are present and unless they are irrigated with blood.

The hypertensive action of the ischemic kidney is independent of the action of the endocrine glands except so far as these glands are necessary to the maintenance of the body in a responsive state.

It has also been demonstrated that the nervous system does not play an essential role in the development of renal hypertension, since

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Renal Ischemia, Surgery **3**:899, 1938. Page, I. H.: The Effect of Bilateral Adrenalectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, Am. J. Physiol. **122**:352, 1938. Collins, D. A., and Wood, E. H.: Experimental Renal Hypertension and Adrenalectomy, ibid. **123**:224, 1938. MacKay, L. L.; Addis, T., and MacKay, E. M.: The Degree of Compensatory Renal Hypertrophy Following Unilateral Nephrectomy: II. The Influence of the Protein Intake, J. Exper. Med. **67**:515, 1938. Verney, E. B., and Vogt, M.: An Experimental Investigation into Hypertension of Renal Origin, with Some Observations on Convulsive "Uraemia," Quart J. Exper. Physiol. **28**:253, 1938. Enger, R.; Linder, F., and Sarre, H.: Die Wirkung quantitativ abgestufter Drosselung der Nierendurchblutung auf den Blutdruck, Ztschr. f. d. ges. exper. Med. **104**:1, 1938. Glenn, F.; Child, C. G., and Page, I. H.: The Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs, Am. J. Physiol. **122**:506, 1938. Glenn, F., and Lasher, E. P.: The Effect of Destruction of the Spinal Cord on the Artificial Production of Hypertension in Dogs, ibid. **124**:106, 1938. Child, C. G., and Glenn, F.: Effect of Passing Renal Blood Through Liver in Dogs with Experimental Hypertension, Arch. Surg. **36**:376 (March) 1938. Wilson, C., and Pickering, G. W.: Acute Arterial Lesions in Rabbits with Experimental Renal Hypertension, Clin. Sc. **3**:343, 1938. Goldblatt, H.: Studies on Experimental Hypertension: VII. The Production of the Malignant Phase of Hypertension, J. Exper. Med. **67**:809, 1938. Katz, L. N.; Mendlowitz, M., and Friedman, M.: A Study of the Factors Concerned in Renal Hypertension, Proc. Soc. Exper. Biol. & Med. **37**:722, 1938.

denervation of the kidneys, total sympathectomy or destruction of the cord below the level of the fifth cervical vertebra does not prevent its development. Furthermore, constriction of the renal artery of a transplanted kidney, free from all nervous connections, leads to an increase in blood pressure.

On the other hand, many experiments are in accord with the fact that renal hypertension is brought about by the liberation of some pressor body by the ischemic kidney.

The search for this pressor substance elaborated by the kidneys goes back forty years to the work of Tigerstedt and Bergman, who demonstrated in extracts of normal kidney a pressor substance to which they gave the name renin. Although this was a major discovery and received some confirmation, it attracted little attention because various investigators, in repeating the tests, obtained doubtful or inconsistent results. There were two chief reasons for this. First, many of the early experiments were carried out on anesthetized animals, and it has been recently shown that the pressor effect of renin is reduced or abolished by anesthetics such as ethyl carbamate (urethane), pentobarbital and ether. Secondly, in preparing renal extracts, precautions must be taken to remove certain depressor substances, or the pressor action of renin will be masked. Better methods have been developed for the removal of depressor substances, and renal extracts can now be prepared which consistently show a good pressor action.

Pickering has stated that renin appears to be a normal constituent of the renal cortex of various animals. In its properties it resembles a protein and is distributed between the euglobulin and pseudoglobulin protein fractions. It is nondialyzable and in neutral solution is destroyed at 60 C. It is insoluble in alcohol, acetone, ether and chloroform and is precipitated by half saturation with ammonium sulfate.

There is some evidence that extracts prepared from ischemic kidneys have a greater pressor action than extracts from normal kidneys. If confirmed, this is important because it suggests that in the ischemic kidney renin is being elaborated in larger amounts. Of greater importance would be the recovery of renin from the circulating blood and demonstration that it is increased in amount when hypertension is present.

There is additional support for the idea that a humoral mechanism is responsible for arterial hypertension in the experiments of Pickering, Prinzmetal and Wilson. They have demonstrated in patients with arterial hypertension that excessive narrowing of the vessels of the hands still remains after removal of vasoconstrictor tone. This strongly suggests that vasoconstriction of humoral origin is present, which dovetails with the results of the studies on experimental hypertension.

Other supporting evidence comes from studies [31] on coarctation of the aorta. In some cases of coarctation, in addition to hypertension in the upper extremities, there is diastolic hypertension in the lower extremities, which indicates a generalized increase in peripheral resistance. Now, it has also been shown [32] that if the aorta of the rat is partially constricted above the point of origin of the renal arteries, hypertension results. This suggests a similarity between the hypertension observed in the patient with coarctation and the hypertension in the rat with constriction of the aorta.

Pressor Responses in Patients with Hypertension.—A number of papers [33] have appeared concerning the effect of various substances or stimuli upon the blood pressure. Of particular interest are the observations of Alam and Smirk. Previously they showed that exercise of the muscles of the forearm performed during arrest of the circulation of the blood to the forearm leads to a rise in the general blood pressure as well as to the production of pain in the exercised muscles. They showed that the rise in blood pressure is reflex in origin and that a definite increase often appears before pain arises. This led to further studies and to an evaluation of the relation between pain of various types and increase in the blood pressure. They found that some sensory stimuli cause much pain but little rise of blood pressure, while others cause less pain but much greater increases of blood pressure. Using cold and exercise of an ischemic limb as stimuli, they studied the blood pressure responses in patients with hypertension and in normal subjects. They found that the effects on both systolic and diastolic pressures are less in patients with renal hypertension than in normal subjects of the same age group. Marked effects on blood

31. Steele, J. M., and Cohn, A. E.: The Nature of Hypertension in Coarctation of the Aorta, J. Clin. Investigation **17**:514, 1938.

32. Rytand, D. A.: The Renal Factor in Arterial Hypertension with Coarctation of the Aorta, J. Clin. Investigation **17**:391, 1938.

33. Alam, M., and Smirk, F. H.: Observations in Man Concerning the Effects of Different Types of Sensory Stimulation upon the Blood Pressure, Clin. Sc. **3**: 253, 1938; Blood Pressure Raising Reflexes in Health, Essential Hypertension, and Renal Hypertension, ibid. **3**:259, 1938. Fatheree, T. J., and Hines, E. A.: The Blood Pressure Response to Epinephrine Administered Intravenously to Subjects with Normal Blood Pressure and to Patients with Essential Hypertension, Am. Heart J. **16**:66, 1938. Ayman, D., and Goldshine, A. D.: Cold as a Standard Stimulus of Blood Pressure: A Study of Normal and Hypertensive Subjects, New England J. Med. **219**:650, 1938. Hardgrove, M.; Roth, G. M., and Brown, G. E.: The Pressor Reaction Produced by Inhalation of Carbon Dioxide: Studies of Patients with Normal Blood Pressure and with Hypertension, Ann. Int. Med. **12**:482, 1938. Elsom, K. A., and Glenn, P. M.: The Pressor Response of Normal and Hypertensive Human Subjects to Tyramine Introduced into the Ileum, ibid. **12**:838, 1938.

pressure were found to occur more frequently in patients with essential hypertension than in normal controls of the same age. Sometimes, however, large rises in blood pressure occurred in normal subjects and small rises in patients with essential hypertension. They concluded that essential hypertension does not usually develop subsequently in healthy subjects with a high reflex reactivity of the blood pressure.

Hypertension in the Pulmonary Circuit.—Staemmler [34] has speculated on the possibility that primary hypertension in the lesser circulation may be the cause of hypertrophy of the right ventricle which cannot otherwise be explained. In regard to thromboendarteritis obliterans, a disorder characterized by the formation and organization of fibrinoid thrombi in the small pulmonary arteries, he arrived at the conclusion that primary hypertension in the lesser circulation must be regarded as the cause. He has also suggested that many instances of pulmonary sclerosis may be due to the same cause. An important argument against this idea, however, is the considerable difference anatomically between the pulmonary and the systemic circulation, there being absent from the former the characteristic arterioles, spasm of which in the latter is probably responsible for the first stage of "primary hypertension."

Treatment.—There are further reports [35] on the surgical treatment of so-called essential hypertension. In general, these reports are optimistic. Undoubtedly the "best results" are obtained in comparatively young persons with variable blood pressure who have not yet exhibited marked vascular changes. In these cases it is to be expected that sympathectomy will cause a fall in blood pressure, as vasoconstriction of nervous (sympathetic) origin constitutes a large fraction of the total peripheral resistance. However, as has been outlined, there is

34. Staemmler, M.: Gibt es eine primäre Hypertonie im kleinen Kreislauf? (Zugleich ein Beitrag zur Frage der sogenannten primären Pulmonal-Sklerose), Arch. f. Kreislaufforsch. **3**:125, 1938.

35. Crile, G.: The Surgical Treatment of Hypertension, Philadelphia, W. B. Saunders Company, 1938. Page, I. H.: Medical Aspects of Surgical Treatment of Hypertension, J. A. M. A. **110**:1161 (April 9) 1938. Goldblatt, H.: Experimental Observations on the Surgical Treatment of Hypertension, Surgery **4**:483, 1938. Rogoff, J. M., and Marcus, E.: Supposed Role of the Adrenals in Hypertension: An Experimental Investigation, J. A. M. A. **110**:2127 (June 25) 1938. Craig, W. M.: Hypertension and Its Surgical Treatment, South. Surgeon **7**:140, 1938. Allen, E. V., and Adson, A. W.: Physiologic Effects of Extensive Sympathectomy for Essential Hypertension: Further Observations, Ann. Int. Med. **11**:2151, 1938. Paliard, F., and Martin, P. E.: Le traitement chirurgical de l'hypertension artérielle permanente: Ses indications par l'infiltration anesthésique des splanchniques, J. de méd. de Lyon **19**:433, 1938. Davis, L., and Barker, M. H.: The Surgical Problem of Hypertension, Ann. Surg. **107**:899, 1938. Lauter, S., and Ott, A.: Ueber die Wirkung des Aderlasses beim Hochdruck, Deutsches Arch. f. klin. Med. **181**:139, 1937.

increasing evidence to show that the abnormal factor in peripheral resistance is probably hormonal, which limits the rationale of the surgical treatment of hypertension to merely a means of removing part of the normal vasomotor control mechanism. Nevertheless, if its usefulness can be proved empirically, it may remain a valuable measure in selected cases.

Massie, Ethridge and O'Hare,[36] in another revival of the thiocyanate therapy, administered the sodium salt according to the method of Barker to 14 patients with hypertension. Barker's method consists essentially in the use of blood cyanate determinations as a guide to proper administration of the drug. Massie and his associates confirmed Barker's favorable results and obtained a significant lowering of blood pressure when the cyanate level of the blood was kept between 5 and 7 mg. per hundred cubic centimeters. Even so, toxic symptoms are occasionally observed, and this method requires careful selection, observation and care of the patient.

BACTERIAL ENDOCARDITIS

The use of sulfanilamide or related compounds in the treatment of subacute bacterial endocarditis is a subject of considerable interest at present. Some verbal reports are very encouraging and provide the basis for new hope. Unfortunately the old difficulty is still present, namely, the inability of any therapeutic agent to reach the living bacteria, which are protected by the mass of fibrin and the corpuscular and bacterial débris which constitute the vegetations. Temporarily the blood stream may be sterilized and a remission of symptoms effected with sulfanilamide, but it is unlikely that more than an occasional cure will result. There is some promise that sulfanilamide may be valuable in gonococcic and pneumococcic endocarditis.

Miles and Gray [37] have described 2 cases of infective endocarditis apparently due to Haemophilus parainfluenzae and have summarized other cases reported in the medical literature in which there may have been a similar pathogenesis. In these cases preexisting valvular damage to the heart has been seldom absent, and the clinical course and autopsy observations do not differ significantly from those in cases of endocarditis due to Streptococcus viridans.

Martin and Adams [38] have described 5 cases of proved syphilitic endocarditis or aortitis with superimposed bacterial vegetations. In

36. Massie, E.; Ethridge, C. B., and O'Hare, J. P.: Thiocyanate Therapy in Vascular Hypertension, New England J. Med. **219**:736, 1938.

37. Miles, A. A., and Gray, J.: Haemophilus Para-Influenzae Endocarditis, J. Path. & Bact. **47**:257, 1938.

38. Martin, H. E., and Adams, W. L., Jr.: Bacterial Endocarditis Superimposed on Syphilitic Aortitis and Valvulitis, Am. Heart J. **16**:714, 1938.

none of these cases were both diagnoses made clinically, but this combination should be considered whenever sepsis of undetermined origin, a positive Wassermann reaction and evidence of aortic insufficiency or of aortitis without evidence of previous rheumatic infection are present.

Recent work [39] on experimental endocarditis has shown that streptococcic endocarditis can be regularly produced in animals and that the infection persists because the surrounding deposits of fibrin afford not only protection from phagocytic cells but an excellent medium for growth. No evidence was observed that the bacterium acquires resistance to the action of white blood cells or that the latter lose their power to destroy the organism.

HEART DISEASE DUE TO CORONARY ARTERIOSCLEROSIS

Pathogenesis.—Moore and his associates [40] have observed a deposition of calcium salts in the yellow elastic fibers of the heart and great vessels of calves fed rations low in magnesium. While these lesions are not typical of arteriosclerotic lesions seen in man, the difference may be due partly to species difference in reaction and to the acuteness of the experiments. They have pointed out that from what is known regarding human requirements for magnesium, deficiency of this element commonly exists in man.

Handovsky [41] fed large amounts of vitamin D to normal dogs and to dogs from which the thyroid and parathyroid glands had been removed. In the latter, macroscopic sclerotic lesions appeared in the aorta, whereas in the former none appeared. When thyroid was given to thyroparathyroprivic dogs, lesions did not appear, which shows the importance of the thyroid function in this regard.

Angina Pectoris.—Starr and his collaborators [42] have made estimations of cardiac output, basal metabolic rate, pulse rate and respiratory rate during and between attacks of angina pectoris. Their results

39. Friedman, M.; Katz, L. N., and Howell, K.: Experimental Endocarditis Due to Streptococcus Viridans: Biologic Factors in Its Development, Arch. Int. Med. **61**:95 (Jan.) 1938. Kinsella, R. A., and Muether, R. O.: Experimental Streptococcic Endocarditis, ibid. **62**:247 (Aug.) 1938. Friedman, M.: A Study of the Fibrin Factor in Its Relation to Subacute Endocarditis, J. Pharmacol. & Exper. Therap. **63**:173, 1938.

40. Moore, L. A.; Hallman, E. T., and Sholl, L. B.: Cardiovascular and Other Lesions in Calves Fed Diets Low in Magnesium, Arch. Path. **26**:820 (Oct.) 1938.

41. Handovsky, H.: Du rôle de la thyroïde et de la parathyroïde dans le développement de l'artériosclérose, Schweiz. med. Wchnschr. **68**:425, 1938.

42. Starr, I.; Gamble, C. J.; Donal, J. S., and Collins, L. H.: Estimations of the Work of the Heart During and Between Attacks of Angina Pectoris, J. Clin. Investigation **17**:287, 1938.

indicate that the work of the heart is significantly greater during the time of the attack and thereby conform to the widely accepted view that cardiac pain is caused by situations demanding increased cardiac work when the blood supply of the heart cannot be increased correspondingly.

Robertson and Katz [43] have described a method for inducing attacks of pain in patients with angina pectoris, which consists of placing an ordinary blood pressure cuff on the left arm above the elbow and inflating it to 50 mm. of mercury above the systolic blood pressure. The inflation is continued for five minutes or until pain is elicited. The test gave negative results in control subjects but positive results in 19 of 24 patients with a definite history of angina pectoris. The possible mechanisms involved are described, and the usefulness of the test is emphasized.

Reid [44] has observed a series of patients in whom the pressure of a cervical rib or of the scalenus anticus muscle on the brachial plexus has been the cause of pain simulating that of angina pectoris. Even precordial pain may be so induced, and some relation to exertion may be manifest. It is pointed out that this syndrome is not rare and that it is important to differentiate it from angina pectoris or coronary thrombosis.

O'Shaughnessy and his associates [45] have described their further experience with cardio-omentopexy. In this procedure a left transpleural exposure of the heart is made, and the left side of the diaphragm is paralyzed by means of crushing the phrenic nerve. An opening is then made in the diaphragm, and a pedicled graft of omentum is brought up and attached to the heart. It has been demonstrated in experimental animals that vascular communications can develop between the omentum and the heart. Twenty patients have been operated on; 15 were suffering from angina pectoris and 5 from other symptoms due to cardiac ischemia. Of the 15 patients who had angina pectoris, 10 were alive six months or longer after the operation; 8 of these 10 had lost the angina and most of them were able to resume profitable activity. Of the 5 patients without angina pectoris, 1 died, while 1 of the remaining 4 became free from symptoms. There was 1 death directly attributable to operation; this resulted from rupture of a friable portion of the cardiac wall. Generally, the operation is attended with little shock, and convalescence is uneventful. O'Shaughnessy's encouraging

43. Robertson, S., and Katz, L. N.: Observations on Referred Pain of Cardiac Origin, Am. J. M. Sc. **196**:199, 1938.

44. Reid, W. D.: Pressure on the Brachial Plexus Causing Simulation of Coronary Disease, J. A. M. A. **110**:1724 (May 21) 1938.

45. Davies, D. T.; Mansell, H. E., and O'Shaughnessy, L.: Surgical Treatment of Angina Pectoris and Allied Conditions, Lancet **1**:1 and 76, 1938.

results with cardio-omentopexy warrant further trial, with careful control studies. The operation may or may not prove to be an advance in the treatment of selected patients with coronary insufficiency.

Coronary Occlusion.—Coronary thrombosis may be properly regarded as a complication of coronary arteriosclerotic disease. Unfortunately, it may occur in persons who present little if any evidence of coronary insufficiency. In other words, these persons might have lived healthy lives for many years if thrombosis with resulting cardiac infarction had not occurred. It is small wonder, then, that great efforts are being made to study not only the underlying atherosclerotic lesion itself but also the various factors connected with thrombosis in a coronary artery. Recent studies embrace the normal vascular supply of large vessels and the development of atheromatous lesions,[46] a new method of studying coronary artery occlusion and anastomoses,[47] the circumstances and precipitating factors under which coronary thrombosis occurs[48] and the problem of "heparin and thrombosis."[49]

Although there is much doubt regarding the vascularity of the intima of normal vessels, there is no doubt about the presence of capillaries in the intima in atherosclerotic lesions, and it has been shown that intimal hemorrhages may result from rupture of capillaries in coronary atherosclerotic lesions. In some instances thrombosis within the lumen of the artery may apparently follow as a secondary effect. However, because intimal hemorrhage occurs so often with complete patency of the adjacent lumen, it is obvious that some additional factor is necessary to initiate thrombosis. It is suggested that this factor is narrowing of the lumen at a point distal to the attachment of the thrombus which provides proper conditions of stagnation and eddying of blood. Paterson considers two principal factors to be involved in the mechanism of capillary rupture, namely, softening by atheroma of the supporting stroma and a high intracapillary pressure. Intimal

46. Winternitz, M. C.; Thomas, R. M., and Le Compte, P. M.: The Biology of Arteriosclerosis, Springfield, Ill., Charles C. Thomas, Publisher, 1938. Leary, T.: Vascularization of Atherosclerotic Lesions, Am. Heart J. **16**:549, 1938.

47. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, Am. Heart J. **15**:528, 1938.

48. Paterson, J. C.: Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis, Arch. Path. **25**:474 (April) 1938. Wartman, W. B.: Occlusion of the Coronary Arteries by Hemorrhage into Their Walls, Am. Heart J. **15**:452, 1938.

49. Best, C. H.; Cowan, C., and Maclean, D. L.: Heparin and the Formation of White Thrombi, J. Physiol. **92**:20, 1938. Solandt, D. Y., and Best, C. H.: Heparin and Coronary Thrombosis in Experimental Animals, Lancet **2**:130, 1938. Best, C. H.: Heparin and Thrombosis, Brit. M. J. **2**:977, 1938. Murray, G. D. W., and Best, C. H.: Use of Heparin in Thrombosis, Ann. Surg. **108**:163, 1938.

capillaries, because they arise directly from the main coronary lumen, are exposed constantly to a relatively high pressure of blood.

Schlesinger has made an important contribution to the study of the anastomoses of normal and diseased coronary vessels. He has described a new method, which consists in cutting the heart so that it can be unrolled and roentgenograms made after the injection of a multicolored opaque medium. In this way the entire course of all the arterial branches can be completely and simultaneously visualized. Schlesinger believes that only in this way is it possible to ascertain accurately the site and the effects of all the occlusions and anastomoses of the coronary arteries. His studies led to the conclusion that the coronary arteries in normal human hearts, even senile hearts, are functionally true end arteries and that anastomotic connections do not develop along with increase in age. He further concluded that anastomoses always develop readily whenever and wherever arteriosclerotic narrowing or occlusion causes obstruction in the coronary circulation.

The recent studies by Best and others on heparin and on blood coagulation are of unusual interest now and may perhaps in the future have great practical importance for the physician and cardiologist. The pure heparin now available is nontoxic and may be administered continuously for days by the intravenous route. It was found that heparin prevented the thrombus formation which normally occurs in the experimental animal after injection of sodium ricinoleate into the lumen of the coronary artery. It is emphasized that the main difficulty in the way of an adequate clinical investigation of the therapeutic possibilities of heparin in acute coronary crises is the absence of premonitory signs of this condition. It is of interest in this connection to note that if coronary thrombosis is usually initiated by capillary hemorrhage, the use of heparin may promote this bleeding as well as act beneficially to prevent thrombus formation. Nevertheless this work stands as a challenge to those interested in this type of heart disease.

There have been a number of papers [50] relating to various clinical aspects of coronary occlusion, a few of which will be briefly reviewed.

50. Master, A. M.; Dack, S., and Jaffe, H. L.: Postoperative Coronary Artery Occlusion, J. A. M. A. **110**:1415 (April 30) 1938. Bean, W. B.: Infarction of the Heart: II. Symptomatology of Acute Attack, Ann. Int. Med. **11**:2086, 1938; III. Clinical Course and Morphological Findings, ibid. **12**:71, 1938. Gorham, L. W., and Martin, S. J.: Coronary Occlusion With and Without Pain: Analysis of One Hundred Cases in Which Autopsy Was Done with Reference to the Tension Factor in Cardiac Pain, Arch. Int. Med. **62**:821 (Nov.) 1938. Martin, S. J., and Gorham, L. W.: Cardiac Pain: An Experimental Study with Reference to the Tension Factor, ibid. **62**:840 (Nov.) 1938. Boyd, L. J., and Werblow, S. C.: Coronary Thrombosis Without Pain, Am. J. M. Sc. **194**:814, 1937. Gold, H.;

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Master, Dack and Jaffe have added proof to the opinion, previously expressed, that there is an association between operations on elderly patients with coronary disease and coronary occlusion. They found that the relatively common occurrence of coronary thrombosis postoperatively stands in sharp contrast to its rare occurrence in the medical wards. Consequently, rest in bed alone is not a factor. Shock, tachycardia, dehydration and infection are mentioned as precipitating factors. Their findings suggest that full consideration should be given to all elderly persons in preparation for operation and that special care should be taken to prevent postoperative shock, dehydration and infection.

Bean has made an excellent study of the underlying conditions predisposing to cardiac infarction, the symptoms of acute attacks, the clinical course and the common sequelae.

Martin and Gorham believe that the incidence of coronary occlusion and cardiac infarction without pain may be much higher than is commonly realized. In an analysis of the clinical histories and necropsy data for 100 patients with cardiac infarction, pain was found to be absent in 42 instances. Boyd and Werblow found that one third of their patients with proved coronary thrombosis manifested no pain. Both reports emphasize that elderly patients are more likely not to have pain; this was borne out in the series of Master, Dack and Jaffe, previously mentioned, wherein a large majority of patients did not suffer pain. Gorham and Martin were impressed with the possible role of a tension factor in the production of pain, and some support for this was obtained in an experimental study on animals. However, it is important to note that the more careful and complete the history in cases of coronary thrombosis, the more often pain or oppression (sometimes misleadingly called "shortness of breath" by the patient) is found to have occurred.

Parkinson, Bedford and Thomson [51] have written an excellent article on cardiac aneurysms. They found that cardiac aneurysms, like infarcts, involve the left ventricle almost exclusively and may best be classified as anterior or posterior, according to the coronary branch

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Modell, W., and Travell, J.: The Influence of the Size of Cardiac Infarcts upon the Electrocardiogram, Am. Heart J. **15**:77, 1938. Laubry, C.; Soulié, P., and Heim de Balsac, R.: Le syndrome phréno-gastrique des coronarites, Arch. d. mal. du cœur **31**:583, 1938. Nichol, E. S.: Large Pericardial Effusion Complicating Acute Coronary Thrombosis, Ann. Int. Med. **11**:1900, 1938. Stewart, C. F., and Turner, K. B.: A Note on Pericardial Involvement in Coronary Thrombosis, Am. Heart J. **15**:232, 1938. Eppinger, E. C., and Kennedy, J. A.: The Cause of Death in Coronary Thrombosis, with Special Reference to Pulmonary Embolism, Am. J. M. Sc. **195**:104, 1938. Hadorn, W.: Ueber kombinierte Thrombo-Embolie der Koronararterien, Ztschr. f. Kreislaufforsch. **30**:563, 1938.

51. Parkinson, J.; Bedford, D. E., and Thomson, W. A. R.: Cardiac Aneurysm, Quart. J. Med. **7**:455, 1938.

occluded. Diagnosis depends mainly on roentgenographic examination. Anterior aneurysms, which form the great majority, cause enlargement of the heart to the left, with deformity of its contour. Posterior aneurysms are best seen in the left anterior oblique view and may displace the esophagus.

Among several articles [52] on the electrocardiographic diagnosis of cardiac infarction, that of Wood and Wolferth on infarction of the lateral wall of the left ventricle is of particular interest. The chief electrocardiographic characteristics are depression of the RS-T interval in lead IV and, usually, depression of this interval in leads I and II, together with absence of the signs of posterior infarction in lead III. They have pointed out that in some patients lateral infarction may not be recognized because the electrocardiographic signs of the lesion may disappear rapidly and completely and because the electrocardiographic pattern may be mimicked rather closely by that due to the action of digitalis or to hypertensive heart disease. However, in only 1 of their cases was the diagnosis confirmed at autopsy.

HEART DISEASE IN RELATION TO THE ENDOCRINE GLANDS

Hyperthyroidism.—Ernstene [53] has made a study of cardiovascular complications in 1,000 consecutive patients with hyperthyroidism. Evidence of organic heart disease was present in 173 patients; in 32 additional patients the heart was enlarged, but no other signs of heart disease were found. It was thought that in the great majority of the latter patients the enlargement was due to simple dilatation incident to the thyrotoxicosis. Auricular fibrillation occurred in 207 patients; in 96 of these the arrhythmia was present before operation, while in 111 it developed for the first time as a postoperative complication. Approximately half of the patients with auricular fibrillation presented evidence of organic heart disease, an incidence about five times that observed in the patients without heart disease. Normal sinus rhythm was reestablished spontaneously in one third of the patients with the continuous form of auricular fibrillation. Quinidine sulfate was administered to half the remaining patients in this group, and normal rhythm was restored in 60 per cent. Although the postoperative mortality was considerably greater for patients who had auricular

52. Wood, F. C.; Wolferth, C. C., and Bellet, S.: Infarction of the Lateral Wall of the Left Ventricle: Electrocardiographic Characteristics, Am. Heart J. **16**:387, 1938. Langendorf, R., and Pick, A.: Zur Diagnose des Myokardinfarktes mit Hilfe von Brustwandableitungen, Acta med. Scandinav. **96**:80, 1938. Bohning, A., and Katz, L. N.: Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion, Arch. Int. Med. **61**:241 (Feb.) 1938.

53. Ernstene, A. C.: The Cardiovascular Complications of Hyperthyroidism, Am. J. M. Sc. **195**:248, 1938.

fibrillation, Ernstene has emphasized that this must not be interpreted as evidence that the arrhythmia per se greatly increases the operative risk but that auricular fibrillation is more common in patients who are poor surgical risks.

Myxedema.—Stewart, Deitrick and Crane [54] have made interesting and important studies on 4 patients suffering from spontaneous myxedema. They found that the myxedematous state was associated with a low basal metabolic rate, with decrease in cardiac output per minute and per beat, with increase in the arteriovenous oxygen difference and with slowing of the velocity of the blood flow. This was a reversible state, since administration of thyroid was associated with alterations toward the normal levels of these functions and with shrinking of the cardiac size. Of particular interest was their observation that the lengthening of the circulation time in myxedema bears a linear relation to the cardiac output and to the oxygen consumption and that the arteriovenous oxygen difference bears a similar relation to the oxygen consumption and to the basal metabolic rate. Thus it appears that in the myxedematous state, even though the circulatory needs of the body are markedly lowered, the heart does not maintain a circulation adequate for these lowered requirements, and greater amounts of oxygen are removed from each unit of blood than normally occurs. This is discussed in the light of the hypothesis of Boothby and Rynearson that in the hyperthyroid state there is present in the organism a special circulatory stimulant which causes a greater increase in the circulation rate than occurs in a normal subject as a result of a corresponding increase in oxygen consumption due to work. In the myxedematous state it may be possible that the opposite is the case.

Acromegaly.—Courville and Mason [55] had occasion to study 24 patients with acromegaly with especial reference to the cardiovascular system both during life and at postmortem examination. In general, the first symptom complained of by these patients is weakness, which is in striking contrast to the great muscular development. As the weakness increases, palpitation and dyspnea on exercise appear and, later, syncopal attacks. As the disease progresses, a striking pallor appears, asthenia becomes extreme, the signs of heart failure increase and finally the patient succumbs. At necropsy the blood vessels are usually enlarged as to both the thickness of the walls and the size of the lumens. The heart may be greatly enlarged, and the enlargement is usually out of proportion to the size of the patient or his muscular

54. Stewart, H. J.: Deitrick, J. E., and Crane, N. F.: Studies on the Circulation in Patients Suffering from Spontaneous Myxedema, J. Clin. Investigation **17**: 237, 1938.

55. Courville, C. B., and Mason, V. R.: The Heart in Acromegaly, Arch. Int. Med. **61**:704 (May) 1938.

development. This hypertrophy may be present in the absence of the usual causes of cardiac enlargement. No constant histologic alteration is present in the myocardium which distinguishes the enlarged heart in acromegaly from other enlarged hearts. The authors conclude that the heart failure is directly related to the acromegalic process.

PERICARDITIS

Acute Pericarditis.—Stewart and his associates [56] have made interesting observations on a young patient suffering from chronic pericardial effusion which appeared to be due to a primary lesion. The patient was not acutely ill and attended school in the intervals between therapeutic pericardial taps. It became apparent that slowly developing cardiac tamponade was responsible for the patient's symptoms, for removal of the fluid resulted in dramatic improvement. It was found that as fluid accumulated in the pericardial cavity in sufficient quantity, the venous pressure rose, the cardiac output became markedly decreased both per minute and per beat, the heart rate increased and the circulation time became longer. When the excess pericardial fluid was removed, these abnormal conditions tended to disappear.

Electrocardiographic changes in pericarditis [57] have continued to receive considerable attention. The comprehensive and critical report of Winternitz and Langendorf is especially noteworthy. Seventy-six cases of pericarditis were minutely analyzed and grouped under the various etiologic factors involved. The electrocardiographic alterations in pericarditis are considered as evolving in four general stages. The characteristic changes in the first stage consist in elevation of the ST segment and the terminal portion of the QRS complex. In the second stage the ST deviation disappears, and the T wave becomes lower in amplitude. In the third stage the T wave becomes negative, while in the fourth stage there is restitution toward the normal. Chest leads were not found to give much positive information, although the absence of change was helpful in the making of the differential diagnosis. Bellet and McMillan, on the other hand, found that the use of leads IV, V and VI was an important aid and that additional information was sometimes obtained by placing the anterior electrode over the area of friction.

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56. Stewart, H. J.; Crane, N. F., and Deitrick, J. E.: Studies of the Circulation in Pericardial Effusion, Am. Heart J. **16**:189, 1938.

57. Winternitz, M., and Langendorf, R.: Das Elektrocardiogramm der Perikarditis, Acta med. Scandinav. **94**:141 and 274, 1938. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis: Evolution, Causes and Diagnostic Significance of Patterns in Limb and Chest Leads; A Study of Fifty-Seven Cases, Arch. Int. Med. **61**:381 (March) 1938.

Chronic Constrictive Pericarditis.—Burwell and Blalock [58] and Stewart and his associates [59] have made careful measurements of various alterations of the circulation in patients with constrictive pericarditis. These alterations include a decrease in cardiac output, in blood velocity and in blood pressure and an increase in venous pressure, in total blood volume and in the heart rate at rest. As a result of these changes the now familiar clinical picture is seen, characterized by dyspnea on exercise, weakness and marked venous congestion, with cough, ascites and edema.

THE HEART IN PREGNANCY

Fetal electrocardiography during pregnancy has been carried out successfully during the past few years. Bell [60] and Strassmann and Mussey [61] have recently reviewed the subject and have published electrocardiograms showing waves undoubtedly of fetal origin. The latter authors have described a simple method which proved successful in recording fetal electrocardiograms in 52 cases during the last seventy days of pregnancy. The chief points in their technic were:

1. The patient is placed flat on her back on a couch. 2. The skin and the electrodes are moistened with saturated saline solution. 3. The electrodes are placed on the upper arms and left thigh. 4. The electrodes then are fastened with bandages 4 inches wide which have been soaked in saturated saline solution. 5. The patient rests ten to fifteen minutes before the electrocardiogram is taken. 6. Tracings are taken with the usual leads (I, II and III). 7. The electrode is changed from left thigh to right thigh. 8. Tracings then are repeated with leads II and III (right arm—right thigh, left arm—right thigh, respectively). 9. Two feet of film should be taken for each tracing. 10. Outside disturbances from other electric apparatus should be guarded against.

The importance of obtaining graphic evidence regarding the viability of the fetus and the rate, rhythm and regularity of the cardiac action is emphasized.

Burwell [62] has found that the major alterations in the circulation of pregnant women include:

(1) An increase in heart rate; (2) a fall in the diastolic blood pressure; (3) an increase in the cardiac output out of proportion to the increase in oxygen con-

58. Burwell, C. S., and Blalock, A.: Chronic Constrictive Pericarditis: Physiologic and Pathologic Considerations, J. A. M. A. **110**:265 (Jan. 22) 1938.

59. Stewart, H. J.; Heuer, G. J.; Deitrick, J. E.; Crane, N. F.; Watson, R. F., and Wheeler, C. H.: Measurements of the Circulation in Constrictive Pericarditis Before and After Resection of the Pericardium, J. Clin. Investigation **17**:581, 1938.

60. Bell, G. H.: The Human Foetal Electrocardiogram, J. Obst. & Gynaec. Brit. Emp. **45**:802, 1938.

61. Strassmann, E. O., and Mussey, R. D.: Technic and Results of Routine Fetal Electrocardiography During Pregnancy, Am. J. Obst. & Gynec. **36**:986, 1938.

62. Burwell, C. S.: The Placenta as a Modified Arteriovenous Fistula, Considered in Relation to the Circulatory Adjustments to Pregnancy, Am. J. M. Sc. **195**:1, 1938.

sumption; (4) an elevated venous pressure in pelvis and legs; (5) a relatively high oxygen content in the blood leaving the uterus; (6) an increase in total blood volume; (7) a loud bruit over the placenta.

Among the many factors in pregnancy which may influence the circulation, Burwell has suggested that two are of particular importance, namely, the obstruction offered by the enlarging uterus to the return of blood from the legs and the large blood supply to the placenta. In regard to the latter, it is emphasized that changes similar to those observed in pregnant women are known to occur in patients with arteriovenous anastomosis. A consideration of the structure of the maternal vascular system in the placenta led to the conclusion that to some degree an arteriovenous leak exists.

MISCELLANEOUS

The Circulation in Pernicious Anemia.—Stewart, Crane and Deitrick [63] have reported their observations on the circulatory responses to decreased oxygen capacity of the blood of 5 patients with pernicious anemia. These observations were first made during the period of anemia and later, after successful treatment. In the anemic state it was found that the stroke volume and the minute volume, the heart rate and the oxygen consumption were in all cases elevated and that the arm to tongue circulation time was decreased. Changes in the reverse direction occurred as the state of the blood approached normal. The venous pressure and electrocardiograms showed no significant alterations during the anemic state. The work of the left ventricle was not increased during anemia; in fact, the work per beat was less. The authors concluded that during the anemic state of pernicious anemia the heart is called on to pump an increased amount of blood per minute and that this is accomplished in part by an increase in the heart rate and in part by the maintaining of a greater output per beat. The red blood cells, though fewer in number, move at an increased velocity and, as a consequence, are used more frequently in the oxygen-carrying capacity.

Heart Failure and Acute Nephritis.—Although it has long been known that heart failure may appear as a complication of acute nephritis, it has remained a rather neglected subject. During the past year a number of articles have appeared which have drawn attention to various clinical aspects of this problem. Langendorf and Pick [64] have critically reviewed the literature on heart failure and nephritis and have presented

63. Stewart, H. J.; Crane, N. F., and Deitrick, J. E.: Studies of the Circulation in Pernicious Anemia, J. Clin. Investigation **16**:431, 1938.

64. Langendorf, R., and Pick, A.: Elektrocardiogramm bei akuter Nephritis, Acta med. Scandinav. **94**:1, 1938.

their own studies, giving particular emphasis to the electrocardiographic alterations. The majority of their patients showed uniform modifications of the electrocardiogram, with a tendency toward discordant changes in the T wave in leads I and III. The full abnormality, not reached in every case, shows an inverted T wave in lead I and a large, pointed T wave in lead III. The T wave in lead IV may become inverted (new terminology), but the R wave remains unaffected, which aids in distinguishing this pattern from that of infarction of the anterior wall of the left ventricle. Displacement of the ST segment, indicative of cardiac infarction or of pericarditis, is not seen. These electrocardiographic alterations are associated in appearance with the rise in blood pressure but not with the clinical signs of heart failure. For this and other reasons the authors concluded that the electrocardiographic modifications observed are due in part to mechanical factors and in part to ischemic or inflammatory changes in the myocardium.

Debré and his co-workers [65] and Rubin and Rapoport [66] have ably discussed the cardiac complications of acute nephritis of childhood. The nephritis may appear insidiously and commonly follows infections of the upper respiratory tract. Cardiac disorders and heart failure were found to be frequent accompanying complications and appeared to be dependent on the extent of the myocardial damage and the degree of hypertension. The manifestations of cardiac involvement embrace the usual signs and symptoms of heart failure. Treatment should include restriction of the intake of fluids, a high carbohydrate diet and the use of magnesium sulfate for the control of hypertension and hypertensive encephalopathy.

Neurocirculatory Asthenia.—Dorst [67] has found that chronic hypoglycemia frequently occurs in asthenic, undernourished patients who present the familiar picture of the "effort syndrome." His suggestion that the hypoglycemia may be partly responsible for the lack of vigor finds some confirmation in the improvement in his patients which followed treatment with small doses of insulin.

Soley and Shock [68] are of the opinion that the symptoms of the effort syndrome can be explained on the basis of respiratory alkalosis resulting from hyperventilation. Experiments on patients have been reported in which the symptoms of the "effort syndrome" were repro-

65. Debré, R.; Marie, J., and Seringe, P.: Le syndrome hypertensif dans les néphrites aiguës de l'enfance, Ann. de méd. **44**:313, 1938.

66. Rubin, M. I., and Rapoport, M.: Cardiac Complications of Acute Hemorrhagic Nephritis, Am. J. Dis. Child. **55**:244 (Feb.) 1938.

67. Dorst, S.: Chronic Hypoglycemia: Problem in Carbohydrate Metabolism, Am. J. M. Sc. **196**:688, 1938.

68. Soley, M. H., and Shock, N. W.: The Etiology of Effort Syndrome, Am. J. M. Sc. **196**:840, 1938.

duced by voluntary overbreathing and relieved after the administration of carbon dioxide. They concluded that the term neurocirculatory asthenia should be discarded and "anxiety state with (or complicated by) the hyperventilation syndrome" substituted. The reviewers are of the opinion that in only certain patients with neurocirculatory asthenia are the symptoms due to hyperventilation and that other factors are frequently responsible for the symptoms.

The Effect of Smoking on the Cardiovascular System.—Thienes and Butt,[69] after analyzing the many reports on the effect of tobacco on the cardiovascular system, concluded that most of the work was improperly controlled and the reasoning highly uncritical. Their own experiments were carefully planned and designed to test the effect of daily injections of toxic doses of nicotine into rats and rabbits. The duration of the experiment was usually between three and six months. They found that vascular degeneration was greater in the control animals than in animals chronically poisoned with nicotine.

Segal [70] and Graybiel, Starr and White [71] have studied the effect of smoking as evidenced in the electrocardiogram. It is shown that in susceptible persons, significant lowering or inversion of the T wave occurs during and for a short period after the inhalation of tobacco smoke. Some proof is offered that these alterations in the T wave are not due to coronary vasoconstriction but to the characteristic action of nicotine on the cardiac ganglions.

Cardiac Trauma.—There have been a number of reports [72] on various aspects of trauma of the heart to which the interested reader may refer for details.

HEART FAILURE AND ITS TREATMENT

Only a few general topics are mentioned under this heading, for the reason that treatment in the various types of heart disease has already been discussed.

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69. Thienes, C. H., and Butt, E. M.: Chronic Circulatory Effects of Tobacco and Nicotine, Am. J. M. Sc. **195**:522, 1938.

70. Segal, H. L.: Cigarette Smoking: I. As a Cause of Fatigue; II. Effect on the Electrocardiogram With and Without the Use of Filters, Am. J. M. Sc. **196**:851, 1938.

71. Graybiel, A.; Starr, R. S., and White, P. D.: Electrocardiographic Changes Following the Inhalation of Tobacco Smoke, Am. Heart J. **15**:89, 1938.

72. Moritz, A. R., and Atkins, J. P.: Cardiac Contusion: An Experimental and Pathologic Study, Arch. Path. **25**:445 (April) 1938. Barber, H.: Trauma of the Heart, Brit. M. J. **1**:433, 1938. Kissane, R. W., and Koons, R. A.: Management and Treatment of Myocardial Contusion, Tr. Am. Therap. Soc. **38**:61, 1938. Kissane, R. W.; Fidler, R. S., and Koons, R. A.: Electrocardiographic Changes Following External Chest Injury to Dogs, Ann. Int. Med. **11**:907, 1938. Elkin, D. C.: The Diagnosis and Treatment of Wounds of the Heart: A Review of Twenty-Two Cases, J. A. M. A. **111**:1750 (Nov. 5) 1938.

Altschule [73] has written an excellent monograph on the pathologic physiology of congestive heart failure. What particularly distinguishes this report from many others is the critical attitude maintained throughout and the absence of any crusading zeal in the support of some favored theory of the pathogenesis of heart failure. The presentation is divided into two parts: The first part deals with an analysis of the physiologic measurements of cardiac decompensation and the second with the interpretation of the physiologic knowledge in explaining the meaning of the cardinal symptoms of congestive failure. This report is recommended to all those wishing to review the present status of the knowledge of congestive failure.

McMichael [74] has shown that in man the normal increase in cardiac output which takes place with a change from the erect to the supine position diminishes and may disappear as cardiac failure progresses. This disappearance of the postural change in cardiac output is due to the inability of the heart to respond to the postural rise of venous pressure. Proof of this was seen when the cardiac output was correlated with the venous pressure in various stages of heart failure. In the early stage of heart failure the cardiac output drops, but the venous pressure remains normal. As the failure increases, the venous pressure rises, and the cardiac output also rises. In the late stages of cardiac failure the output falls below normal, despite a progressive rise of the venous pressure. These findings suggest the interesting probability that the increase in venous pressure associated with heart failure, rather than being a passive phenomenon depending on diminution of the cardiac output, is in the nature of a compensating mechanism which maintains the output of the heart at a higher level. This interpretation would explain many puzzling facts of cardiac behavior in congestive failure.

The amount of investigation and the sharp differences of opinion in regard to the therapeutic action of digitalis suggest that this drug has just recently been released for clinical trial. Moe and Visscher [75] have pointed out that the various methods of biologic assay now in use all involve determinations of the toxic dose of digitalis, with the tacit assumption that the therapeutically useful properties will vary in direct proportion to the toxic ones. They believe there is much evidence that this premise is incorrect, and, accordingly, they have studied the activity

73. Altschule, M. D.: The Pathologic Physiology of Chronic Cardiac Decompensation, Medicine **17**:75, 1938.

74. McMichael, J.: The Output of the Heart in Congestive Failure, Quart. J. Med. **7**:331, 1938.

75. Moe, G. K., and Visscher, M. B.: Studies of the Native Glucosides of Digitalis Lanata with Particular Reference to Their Effects upon Cardiac Efficiency and Their Toxicity, J. Pharmacol. & Exper. Therap. **64**:65, 1938.

of the separate pure native glucosides of Digitalis lanata on the basis of their physiologically useful properties. They have determined for the dog the minimum doses producing increased cardiac efficiency and those causing irregularities in rhythm. It was found that the ratio of the dose causing increased cardiac efficiency to the dose producing irregularities differs greatly for the different glucosides. The importance of this method of study is emphasized.

Katz and his associates[76] have studied the effect of digitalis on the dog, and their results indicate that this drug has no direct influence on the contractile powers or mechanical efficiency of the cardiac muscle, either in the "physiologic" or in the failing heart. They found that the chief if not the sole site of action of therapeutic doses of digitalis is on the peripheral vessels, especially those of the liver. In the animals with low arterial blood pressure there was an additional indirect effect on the heart due to improvement of the coronary flow by virtue of its pressor effect on the blood pressure. Cattell and Gold,[77] on the other hand, have demonstrated that in the isolated papillary muscle from the cat, digitalis bodies have a direct effect in increasing systolic tension. This increase was found to be independent of any effects which might be mediated through other influences on the intact heart. They concluded that shortening of the muscle fiber (decrease in diastolic size) is not essential to the explanation of the action of digitalis in increasing the force of contraction of the failing mammalian heart.

Stewart and his associates,[78] on the basis of clinical studies, believe that although digitalis acts directly on the cardiac muscle, the effect on systolic tension is not the most important. They consider the decrease in cardiac size to be the most significant effect of the drug and that the change in cardiac output is largely a consequence of this. Thus, in a normal person digitalis decreases the cardiac output and the cardiac size, even though there is reason to believe that the extent and the force of ventricular contraction increase. In other words, the effect on size in making the pump too small is the predominate one and results in a decrease in output. It was found that in the patient with heart failure, digitalization usually causes a reduction in the size

76. Katz, L. N.; Rodbard, S.; Friend, M., and Rottersman, W.: The Effect of Digitalis on the Anesthetized Dog: I. Action on the Splanchnic Bed, J. Pharmacol. & Exper. Therap. **62**:1, 1938. Katz, L. N., and Mendlowitz, M.: Heart Failure Analyzed in the Isolated Heart Circuit, Am. J. Physiol. **122**:262, 1938.

77. Cattell, M., and Gold, H.: The Influence of Digitalis Glucosides on the Force of Contraction of Mammalian Cardiac Muscle, J. Pharmacol. & Exper. Therap. **62**:116, 1938.

78. Stewart, H. J.; Deitrick, J. E.; Crane, N. F., and Wheeler, C. H.: Action of Digitalis in Uncompensated Heart Disease, Arch. Int. Med. **62**:569 (Oct.) 1938.

of the heart but that the accompanying change in cardiac output depends largely on the initial size of the heart. In the patient with an enlarged heart and congestive failure the output increases, while in the patient with a normal-sized heart and slight symptoms the output may increase, decrease or remain the same. However, the work of the heart per beat was found to be increased by digitalis in all types of heart disease, whether failure was present or not and whether there was auricular fibrillation or normal rhythm. The main conclusion of this work has been supported by the results of Starr and his associates,[79] who found that regardless of whether the cardiac output is increased or decreased, digitalis stimulates the heart in every instance; i. e., the work of the heart per beat in proportion to its size increases. This indicates that digitalis not only may benefit patients in congestive failure with cardiac enlargement but also may benefit certain patients with heart disease but without appreciable heart failure.

79. Starr, I.; Gamble, C. J.; Margolies, A.; Donal, J. S., Jr.; Joseph, N., and Eagle, E.: A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size: On Respiration, on Metabolic Rate and on the Electrocardiogram, J. Clin. Investigation **16**:799, 1937.

News and Comment

Graduate Fortnight of the New York Academy of Medicine.—The twelfth graduate fortnight of the New York Academy of Medicine will be held from Oct. 23 to Nov. 3, 1939. The purpose is to make a complete study and authoritative presentation of a subject of outstanding importance in the practice of medicine and surgery—the endocrine glands and their disorders. The following topics are listed: "Historical sketch of the development of endocrinology; physiology of anterior lobe of pituitary gland; hyper and hypopituitarism; pituitary diencephalic syndromes; physiology of the ovaries; physiology of testes and therapeutic application of male sex hormones; puberty, menstruation and menopause; pregnancy; therapeutic application of female sex hormones; physiology of the parathyroid; hypo and hyper-parathyroidism; the adrenal cortex; the Cushing syndrome: neoplasms of adrenal and their clinical relations; overfunction of the adrenal cortex; the adrenal medulla; adrenal insufficiency; relation of diabetes to endocrine system; relationship of endocrines to nervous system; the physiology and principle inter-relations of the thyroid; hyperthyroidism and hypothyroidism; surgical treatment of hyperthyroidism and other diseases of the thyroid gland."

A carefully integrated program will be presented which will include clinics and clinical demonstrations at many of the hospitals in New York, evening addresses and appropriate exhibits. The evening sessions at the Academy of Medicine will be addressed by recognized authorities in their special fields, drawn from leading medical centers of the United States. The comprehensive exhibit will include books and roentgenograms, pathologic and research material and presentations of clinical and laboratory diagnostic and therapeutic methods. It is also planned to provide demonstrations of exhibits.

All members of the medical profession are eligible for registration. A complete program and registration blank may be secured by addressing Dr. Mahlon Ashford, The New York Academy of Medicine, 2 East 103rd Street, New York.

Book Reviews

The Collapse Therapy of Pulmonary Tuberculosis. By John Alexander, M.A., M.D., F.A.C.S., Professor of Surgery of the University of Michigan; Surgeon-in-Charge of the Division of Thoracic Surgery, Department of Surgery, University of Michigan Hospital. With contributions by the following: Max Pinner, M.D., F.A.C.P., Herman M. Briggs Memorial Hospital, Ithaca, N. Y.; Principal Diagnostic Pathologist, District Tuberculosis Hospitals, New York State Department of Health; John Blair Barnwell, M.D., Associate Professor of Internal Medicine, University of Michigan; Physician-in-Charge of the Tuberculosis Unit of the Department of Internal Medicine, University of Michigan Hospital; Kirby Smith Howlett Jr., M.S., M.D., Resident, Laurel Heights State Tuberculosis Sanatorium, Shelton, Conn. Price, $15. Pp. 705, with 367 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

Strictly, the title of this book is a misnomer. The author, together with the contributors, not only has considered those procedures which involve collapse of the lung but has completely covered the field of surgical treatment of pulmonary tuberculosis. The operative procedures are considered in the following order: paralysis of the phrenic nerve, scaleniectomy and scalenictomy, pneumothorax, intrapleural pneumonolysis, oleothorax, paralysis of intercostal nerves, extrapleural pneumonolysis, subperiosteal and subcostal pneumonolysis, thoracoplasty, surgical drainage of the pulmonary cavity and surgical treatment of tuberculous empyema and tuberculosis of the thoracic wall. Each of the procedures is considered in detail. The indications and contraindications, the surgical technic, the preoperative and the postoperative care and the complications are discussed carefully and at length. When multiple operations are necessary the order and time of their performance are carefully set out.

Excellent photographs and drawings are used liberally, and equally good roentgen reproductions are most helpful. In addition, there is a review of the entire subject of collapse therapy, and a description is given of its development to the present. Most helpful also is the excellent discussion of the physiologic principles of collapse therapy and the pathology of pulmonary collapse. The book may be read with great profit by any one interested in the treatment of pulmonary tuberculosis, be he surgeon or internist.

In spite of his enthusiasm for surgical treatment, the author tries to maintain a balanced point of view. He repeatedly warns against surgical intervention unless the proper indications are present. He calls attention to the good results obtained in cases of minimal involvement when well regulated treatment is given in a sanatorium, without surgical intervention. But when one reads that 96.7 per cent of the patients in residence in one of the sanatoriums from which much of the material is drawn have had some sort of collapse therapy, one wonders if all the warnings have been heeded. It is doubtless true that certain surgical measures do no harm in cases of minimal involvement even when they might have been avoided. But this is true only when the surgical treatment is carried out by thoroughly competent surgeons.

The author speaks of the inadvisability for a physician to attempt collapse therapy until he has had adequate surgical training. Might it not be in order to protest against the attempt by the surgeon to treat pulmonary tuberculosis until he has had sufficient medical training in the evolution of this disease? Arguments of this sort are bound to involve matters of personal opinion, and while it seems that the pendulum has swung just a little too far toward the surgical side, this fact should not militate against the excellence of this book as a treatise on the surgical management of pulmonary tuberculosis.

The Construction of Vulcanite Applicators for Applying Radium to Lesions of the Buccal Cavity, Lips, Orbit and Antrum. By Desmond Greer Walker, M.A., M.Dent.Sc., M.B., B.Ch.; Dental Registrar at the Middlesex Hospital. Price, 5s. Pp. 61, with 12 illustrations. London: Middlesex Hospital Press, by John Murray, 1938.

This monograph does not pretend to do more than discuss the technic for the preparation of radium applicators to be used in and about the mouth. It is taken for granted that the application of a radium pack has been chosen as the method of treatment and that the actual dose to be used has been prescribed by the radiotherapist.

If one is tempted to criticize the author's methods as unduly elaborate, one need only reflect that the proper geometric arrangement and fixation of radium applicators is a prime factor on which success or failure in the cure of cancer may often rest. One cannot be too meticulous in this regard. The construction of accurate models also provides permanent records of original lesions which may prove invaluable.

The author rightfully stresses the great importance of spacing in the protection of normal structures and recommends the use of lead for further protection. It should be made clear that in cases in which the use of lead is indicated, a thickness of 0.5 cm. or more is necessary to be really effective. In many cases the use of lead may be rendered entirely unnecessary by effective spacing.

The text is particularly well illustrated. It should be of interest to any one called on to treat cancer of the oropharynx.

The Harvey Lectures. Series 32. Delivered under the auspices of the Harvey Society of New York, 1937-1938; under the patronage of the New York Academy of Medicine. By various authors. Price, $4. Pp. 275, with 79 charts and illustrations. Baltimore: Williams & Wilkins Company, 1938.

All who are acquainted with previous *Harvey Lectures* will find no occasion for surprise in the statement that the present series meets the same high standard set up by its predecessors. Each lecture is the exposition of an original piece of work carried out by the lecturer and is accompanied by an adequate bibliography dealing with the subject under discussion. Here is a source of original information for all who may have an interest in the subjects presented. The titles and the names of the authors are as follows: "The Nature of the Visual Process," by Dr. Selig Hecht, professor of biophysics, Columbia University; "The Pasteur-Meyerhof Reaction in Muscle Metabolism," by Dr. Einar Lundsgaard, professor of physiology, Institute of Medical Physiology, University of Copenhagen; "The Functional Significance of the Lymphatic System," by Dr. Cecil K. Drinker, professor of physiology, Harvard University; "Transfers of Water and Solutes in the Body," by Dr. John P. Peters, professor of medicine, Yale University; "Studies on the Cortical Representation of Somatic Sensibility," by Dr. Philip Bard, Johns Hopkins University; "The Isolation and Properties of Tobacco Mosaic and Other Virus Proteins," by Dr. Wendell M. Stanley, associate member of the Rockefeller Institute for Medical Research, Princeton, N. J.; "The Chemistry and Biology of Male Sex Hormones," by Dr. F. C. Koch, professor of biochemistry, University of Chicago; "Experimental Hypertension Induced by Renal Ischemia," by Dr. Harry Goldblatt, professor of experimental pathology, Western Reserve University.

Bienengift als Heilmittel. By Robert Schwab. Price, 2.40 marks. Pp. 48. Leipzig: Georg Thieme, 1938.

The recent use of the poison of the honey bee in the treatment of patients suffering from the various forms of arthritis or neuralgia and the reports of the striking benefit resulting from such treatment have stimulated an interest in this therapeutic measure. Previous publications on the subject have been disappointing

because of the lack of sufficient detail in the description of cases and the absence of a critical analysis of the results obtained. One picks up the present monograph with the hope that an adequate appraisal of bee venom as a remedy has at last been made. One finds, however, that the author has devoted twenty-two of the thirty-five pages that are directly on the subject to a discussion of the history of the use of bee venom in medicine, a discussion of animal venoms in general, a recounting of the physiologic action of the venom and a consideration of the question of immunity to it. The second part, which consists of twelve pages, is devoted to treatment with the venom of the honey bee. Much of the material is concerned with the work of others. The author used a salve containing bee venom in a total of 160 cases that were listed as follows: "acute as well as primary and secondary polyarthritis, arthritis deformans, myalgia, acute and chronic muscular rheumatism and . . . neuritis and neuralgia." He reports that the best results were obtained in cases of neuralgia, neuritis and myalgia.

The reader finishes the book with the conviction that a critical evaluation of honey bee venom as a therapeutic agent is still to be written.

A Textbook of Hematology. By William Magner, M.D., Pathologist, St. Michael's Hospital, Toronto, Canada, and Lecturer in Pathology, University of Toronto. Price, $4.50. Pp. 395, with 29 tables and illustrations. Philadelphia: P. Blakiston's Son & Co., 1938.

The author has written this book with a dual purpose in mind: to present the subject of hematology to practicing physicians in a manner that is readable and also to present technics and data to those primarily interested in the study of disease by laboratory methods.

The volume is engagingly written and well illustrated with good colored plates, photomicrographs and charts. At the end are a well chosen bibliography and a comprehensive index. The entire book is constructed along workmanlike lines and is handsomely printed.

That the practicing physician will find it useful is self evident. The various clinical implications of modern hematology are well expressed, and the importance of the proper use of recently developed methods for studying and classifying the various disorders of the blood are explained in an interesting way. The laboratory worker—especially the student or teacher—also will like it. Technics, the fine points in differential diagnosis and classification of blood cells or blood dyscrasias and the terminology of the modern hematologist are all clearly described.

On the whole, therefore, this new manual on hematology is a useful adjunct to any medical library. The author is to be congratulated on having put together such a pleasing textbook.

Immune-Blood Therapy of Tuberculosis. By Joseph Hollós. Price, $2. Pp. 197. New York: Privately Printed, 1938.

Blood from rabbits "immunized" with a bouillon culture of human and bovine tubercle bacilli is hemolyzed, deproteinized and diluted (1:100,000). This material's "faculty of dissociation is so considerable that it shows several ions. . . ." The stock solution is diluted further in a truly homeopathic manner, and therapy is generally started with a few minims of dilution 9 (1:1,000,000,000). This dilution of "immune-blood" may be rubbed in, injected or drunk—miraculous results ensuing regardless of the mode of exhibition. The results are documented by an amazing series of case reports, remarkable chiefly for a lack of specific detail. The whole unscientific mess is preceded by an introduction in which the author details his "persecution" by medical groups, first in Europe, now in America. Wistfully and unsuccessfully he compares his lack of recognition to the treatment of Semmelweis by his contemporaries!